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# THE ACTION OF OILS IN THE PRODUCTION OF TUMORS

## WITH A DEFINITION OF THE CAUSE OF CANCER *

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In 1906 B. Fischer introduced drops of a saturated solution of scharlach r in olive oil directly under the epidermis of the ears of rabbits. He notes that the epithelial cells grew down to surround these oil droplets. The histologic picture of this growth of the epithelial cells resembled epitheloid cancer in many cases, but these formations always ceased to proliferate and regressed after a time. Reinke introduced drops of ether into the eye of salamanders. A growth of cells was induced by the presence of this substance. He transplanted this new growth to the peritoneal cavity and found it continuing to proliferate for a time. White succeeded in inducing epithelial activity with drops of oleic acid, and Strober and Wacker with sudan III, indol and skatol. Benthin used several such materials, and Bullock and Rohdenberg and others have tried the effect of introducing scharlach r into various internal organs. In each instance these authors noted the same result: an encompassing of the oil with cells, certain grades of degeneration and proliferation, then a gradual regression of the newly formed tissue.

While there seemed little doubt from these experiments, as Wacker and others have pointed out, that certain lipoid solvents may excite epithelial growth, there was no evidence that they could excite true cancer.[1] On the other hand, it had long been known that certain workers exposed continuously to the action of soot (chimney sweeps [2]) and the action of other coal tar products are particularly predisposed to develop cancers of the skin, and that these individuals develop their cancers in localities of the skin where the soot or other substances are present frequently over a long period of time. Yamagiwa, appreciating

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1. Ewing, J.: Neoplastic Diseases, Ed. 2, Philadelphia, 1922.
2. Potts, P.: Surgical Observations, London, 1775.

the significance of the observations of B. Fischer and the relation of these observations to the development of cancer in coal tar workers, noticed that the difference between the experiments performed and the development of cancers in men exposed to lipoid solvents is that the animals studied received only a single dose while the men developing cancer were often irritated repeatedly by these substances for many years before their cancers appeared.

Yamagiwa and Ichikawa [3] then undertook the study of the effect of repeated applications of coal tar to certain restricted areas of the skin of the ears of rabbits. They found a piling up and proliferation of the epithelial cells of the skin after each application. Very large papillomas developed in some instances. In others the tissue not only suffered proliferation but also an associated degeneration and ulceration after each application of the tar. Eventually many of these tumors became cancers and metastasized. Since that time many workers have succeeded in producing carcinomas by repeatedly painting coal tar on certain areas of the skin of rats and mice (Woglom and Murray,[4] Fibiger,[5] Deelman,[6] Lipschitz [7] and others). Other similar substances, such as sudan III in olive oil and paraffin oil, have also given similar results. How these substances act to produce this disease has not, however, been fully explained. Clowes [8] suggested that these substances may act to initiate growth by dissolving the lipoid membrane of the cell. Bullock and Rohdenberg [9] thought that these substances acted to destroy the cells. They noted that many cells coming in contact with the tar degenerated. They considered that the growth followed this primary death of the cells. Champy [10] has outlined a similar theory. He concludes that the primary action of the tar is a destruction of cells. Other cells then grow to replace the defect from this loss of cells. The cells thus continuously stimulated to regenerate finally acquire the property of independent growth.

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3. Yamagiwa, K., and Ichikawa, K.: Experimental Studies on the Pathogenesis of Cancer, J. Cancer Res. **3**:1 (Jan.) 1918.

4. Woglom, W. H., and Murray, J. A.: Experimental Tar Cancer in Mice, Seventh Sc. Rep. Imperial Cancer Res. Fund, London, 1921, p. 49.

5. Fibiger, J.: Etat actuel des recherches sur la production experimentale du cancer, les buts de ces recherches et les problemes qui en preunent leur origine, Acta chir. Scandinav. **55**:343, 1922.

6. Deelman, H. T.: Ueber die Histogenesis des Teerkrebses, Ztschr. f. Krebsforsch. **19**:125 (Oct.) 1922.

7. Lipschitz, B.: Unterschungen uber die Entstchung des experimentellen Teercarcinoms der Maus., Ztschr. f. Krebsforsch. **21**:50, 1923.

8. Clowes, G. H.: Tr. XVII Internat. Cong. Med., London, 1913.

9. Bullock, F. D., and Rohdenberg, S. L.: A Study of the Scharlach R Reaction and of Allied Forms of Epithelial Proliferation, J. Med. Res. **33**:53, 1915.

10. Champy, C., and Vasilin, I.: Recherches sur le cancer experimental du goudron, Bull. du Cancer **12**:111, 1923.

Other authors have searched for specific substances in the tar. Several by-products of tar have been isolated and studied. Kennaway [11] states that isoprene causes cancers to develop more readily than coal tar. Other substances also have been isolated and studied. Kennaway, in one of his analyses, finds that the viscid tar of horizontal retorts is more active than the tar distilled in vertical ones, and that certain by-products of tar are more active than others.

It must be pointed out here that the more recent and older work on cancer has shown that it may not only be induced by coal tar and other lipoid solvents, but also by a number of different conditions and substances, such as roentgen rays, radium, certain animal parasites [12] and bacteria; that it may follow long standing chronic inflammation, atrophy from any cause, congenital tumor and defects, and probably in certain instances other injurious agents. In many of these studies, it has also been shown that these substances are not responsible for the eventual course of this disease but are important only in inducing it. Cancer is evidently not a disease to be classed with the infectious diseases [13] but is an active, independent growth of body cells. This primary growth is the result of some primary change either in the cell or in the tissue which may be induced by any one of the various substances or conditions mentioned above. When this change is once established, the cells then continue to grow indefinitely at the expense of the organism and independent of the causative agent. While it is true that Yamagiwa and Ichikawa [3] and later authors have shown quite definitely that coal tar repeatedly applied to areas of the skin will produce cancer, the cancers once induced have in each instance then proceeded independently of the tar. Many of these have been transplanted repeatedly to other animals and have continued to grow actively long after the tar had completely disappeared. The same is true of the cancers induced by animal parasites. Several years ago, Edwin Smith [14] isolated a bacterium, *B. tumefaciens*, from a cancerous growth in a plant. This organism is easily cultivated in a nutrient medium and will induce cancers when injected into other plants. Recently, Blumenthal, Auler and

11. Kennaway, E. L.: Cancer Producing Substances from Isoprene, J. Path. & Bacteriol. **27**:233 (July) 1924; On Cancer-Producing Tars and Tar-Fractions, J. Indust. Hygiene **5**:462 (April) 1924.

12. Fibiger, K.: On Spiroptera Carcinomata and Their Relation to True Malignant Tumors, with Remarks on Cancer Age, J. Cancer Res. **4**:367, 1919. Bullock, F. D., and Curtis, M. R.: The Experimental Production of Sarcoma of the Liver of Rats, Tr. New York Path. Soc. **20**:149, 1920.

13. Burrows, M. T.: Is Cancer a True Disease or Merely the Result of a Change in the Organization of the Organism? Radiology **4**:407, 1925.

14. Smith, E. F.: Studies on the Crown Gall of Plants, Its Relation to Human Cancer, J. Cancer Res. **1**:231 (April) 1916.

Paula Meyer [15] and Nuzum [16] have isolated several organisms from human cancers. One of the organisms isolated by the German authors resembled *B. tumefaciens.* Others were cocci. They found *B. tumefaciens* capable of inducing cancers in both plants and lower animals. The other organisms they have isolated have produced cancers in lower animals.

All malignant tumors do not contain such organisms. Even the most malignant tumors are often free from them. We have sought in vain to demonstrate bacteria in a rat sarcoma now being propagated in the laboratory. Jensen,[17] in studying the plant cancers induced by *B. tumefaciens,* has found that the bacteria are probably unimportant in doing more than inducing the cancer as coal tar, the roentgen ray and radium induce it. He found that these bacteria may disappear in these tumors after a time, although the tumor itself may be growing as actively as before. There is no evidence that the growth of the cancer induced by the action of roentgen ray and radium is due to the continuous action of the rays but to changes in the cells or tissues primarily induced by them. The same is true for the cancers of the stomach induced by the spiroptera [18] and the sarcomas noted by Bullock and Curtis [19] to form about the larva of the cat tapeworm in the liver of rats. The cancers proceed but these organisms always disappear.

The problem to be solved in the study of the action of coal tar and other lipoid solvents on the tissue is the nature of this change induced either in the cell or in the environment that allows the cells to grow independently. This problem cannot be solved through a study of the physical and chemical properties of these lipoid solvents alone, but will become understood only through a broadening of our knowledge of those general conditions which control cellular activity in the normal organism. The organism is a mass of cells. It has come about through a definitely regulated growth of the egg cell and the formation of the different types of cells. This organism matures and functions through a gradual change in the cells so that they use their energy for function rather than for growth. This organism maintains itself for a given period of time in that enough energy is used for growth to take care of the destruction suffered by the cells in their function.

There has never been any evidence to show, however, that the functioning body cells may not under the proper conditions utilize their

15. Blumenthal, Ferdinand; Auler, H., and Meyer, Paula: Ueber das Vorkommen Neoplastischer Bakterien in Menschlichen Krebsgeschwulsten, Ztschr. f. Krebsforsch. **21**:26, 1924.

16. Nuzum, J. W.: Experimental Primary Epithelioma from Micrococcus, Surg., Gynec. & Obst. **40**:343 (March) 1925.

17. Jensen, cited by Blumenthal (Footnote 15).

18. Fibiger: (Footnote 12, first reference).

19. Bullock and Curtis: (Footnote 12, second reference).

entire energy for growth. It is evident that in such a colony of cells as the body of man, in which the cells as a mass are using their energy for function, if one cell breaks away from the conditions that force it to function and acquires the property of independent growth, it must soon destroy its neighbors weakened by their functional burdens.

These recent researches have, therefore made the study of the action of oils in the production of cancer and the whole cancer problem one of the most fascinating and most hopeful for the development of broad biologic generalizations. The cancer problem as it is known today deals with those fundamental processes which regulate the normal growth, function and death of the organism.

Many of the earlier authors had already appreciated that cancer is an independent growth of body cells, a parasitism of one cell or a group of cells on their neighbors forced to work for the whole rather than acquire nutrition and use it for their own development. In attempting to explain it as such, certain of these writers thought that the control exercised by the whole over the growth and function of the cells was associated with permanent irreversible age changes in the physical and chemical structure of the cell. They looked, therefore, at the cancer cell as a cell that had become changed. It is a specially differentiated cell. The cancer cell arising from the skin epithelium differs from the skin in the same general manner as the skin epithelial cells differ from the muscle cells.

There was another group of authors among whom Ribbert[20] was preeminent, who took quite a different view. They looked at the active growth in cancer as the result of primary changes in the environment about the cells rather than in the cell itself. Ribbert based his argument on the fact that there is no evidence that the cells of the body lose their power to grow during development or in later life. That wounds heal readily in old persons and that the tissues of these old persons may regenerate prove this fact conclusively. The stopping of growth at maturity is the result of the acquired organization of the whole or the environment about the cells, and is not due to any irreversible age change in the cell.

In further proof for this deduction came the experiments of Driesch,[21] those of many other students of development, and the more careful analysis of the peculiarities of the cancer cells on which the adherents to the idea of a specially differentiated cancer cell clung. Driesch had noted that when a sea urchin gastrula is bisected, each half will regenerate into a complete sea urchin embryo and adult. These

20. Ribbert, H.: Das Karzinom des Menchen, sein Bau, sein Wachstum, seine Entstehung, Bonn, 1911.

21. Driesch, H.: Die Localization morphogenetischer Vorgange, Arch. f. Entwcklngsmechn. d. Organ. **8**:35, 1899.

bisected halves do not begin to grow at once, however, but only after each has reformed by a shifting of cells into a perfect gastrula of one-half the normal size. The embryonal cells of the gastrula do not grow under all conditions. When the gastrula is bisected, they show only migration. Only when a special form is obtained in the whole does the growth of the cells again intervene. Again many students of cellular growth and cell division have shown that these acts may be initiated by outside means or by changing the environment, and that they are controlled definitely by the environment and not by the cell in the normal organism.[22]

The chief arguments that the cancer cell is different from the normal cell are that it has a different shape, it grows independently, it stains differently, its mitotic figures may be irregular and it may contain inclusions. Each one of these peculiarities has now been shown to be easily reproduced by simply changing the environment about any normal cell. The body cell is a fluid system that can be easily molded. Its shape is determined entirely by its outside contacts.[23] Any normal cell growing in the proper environment may take up foreign matter, may divide irregularly as cancer cells divide, and may stain as cancer cells stain. Wilson has shown that a substance that induces the unfertilized egg to develop normally will induce abnormal mitosis in eggs if allowed to act too long or in too great concentrations.[24]

While Ribbert and the schools proceeding and following him were unable to ascertain the nature of the environment suitable for cells to grow independently, the weight of evidence has always been with them in spite of the fact that a large majority of workers in this field have taken the other view. This flocking of the larger school to the standards of a different type of cells in cancer has not been, evidently, from an analysis of the facts at hand, but from the greater influence of men like Cohnheim and other leaders in pathology. The embryonal theory of cancer was apparently too fascinating. They refused to leave it and admit that cancer cells arising from the epidermis are nothing more than independently growing epidermal cells.

It remained, therefore, to find some means to isolate normal living body cells and study their habits in various kinds of environments. Reverdin had shown that small pieces of skin removed to a wounded surface grow and later attach themselves to the normal organism and aid

22. Wilson, E. B.: The Cell in Development and Heredity, Ed. 3, New York, p. 1029.

23. Burrows, M. T.: Energy Production and Transformation in Protoplasm as Seen Through a Study of the Mechanisms of Migration and Growth in Body Cells, Am. J. Anat., to be published.

24. Wilson, E. B.: Experimental Studies in Cytology, a Cytological Study of Artificial Parthenogenesis in Sea-Urchin Eggs, Arch. f. Entwcklngsmechn. d. Organ. **12**:529, 1901.

in covering the defect. Hertzler studied these skin grafts carefully to find that they take only when they are placed on a surface covered with a layer of clean fibrinous exudate. They grow into this exudate to make firm union with the body later.[25] In 1905 Harrison had noted that when the neural tube of young frog embryos is placed in a thin layer of lymph on the surface of a cover glass in a moist air chamber that the cells migrate and nerve fibrils grow from them into the clotted lymph. No actual growth of cells was noted, however, in these cultures by Harrison.[26]

The senior author, having the opportunity to work with Dr. Hertzler while he was performing his experiments on the healing of wounds in the peritoneum and skin grafting, appreciated at a latter date that the cells which grow first from the Reverdin skin grafts, grow quite independently of the body. Hertzler found that these grafts take only when the wound is covered by a layer of fibrin. In many such cases the grafts are separated from the underlying blood vessels by this fibrinous layer. Since substance diffuses poorly into such fibrinous layers, the cells migrating into the exudate from these fragments must be cut off largely from the body. These cells should grow readily, therefore, when removed to a layer of fibrinous exudate outside the body. In the summer of 1910, under a grant by the Rockefeller Institute, the senior author commenced to study the cultures of Harrison in his laboratory and attempted to develop a method for cultivating the tissues of higher animals. Blood plasma was first substituted for the lymph used by Harrison. In thin layers of plasma suspended from a cover glass into a small moist air chamber, the cells were found to grow readily and actively in many cultures of fragments of chick embryos.[27] These cells, it was interesting to note, did not grow in every culture of fragments of the same tissue placed in layers of the same medium, and where growth intervened the cells did not tend to arrange themselves into organ structures peculiar to their growth in the body, but they invaded the medium along the lines of least resistance, exactly as cancer cells grow and invade the organism. It seemed evident, therefore, that the secrets of the problem of cancer lay hidden in the conditions that allowed these cells to grow in this fashion in these cultures, or in the environment that the cultures

25. Hertzler, A. E.: The Peritoneum, Chapter V, **1**, 1919.

26. Harrison, R. G.: The Outgrowth of the Nerve Fiber as a Mode of Protoplasmic Movement, J. Exper. Zool. **9**:787, 1910.

27. Burrows, M. T.: Culture des Tissus d'embryon de Poulet et specialement cultures de nerfs de Poulet en dehors d l'organisme, Comp. rend. Soc. de biol. **2**:291, 1910; The Cultivation of Tissues of the Chick-Embryo Outside the Body, J. A. M. A. **55**:2057, 1910; The Growth of Tissues of the Chick-Embryo Outside the Animal Body, with Special Reference to the Nervous System, J. Exper. Zool. **10**:63, 1911.

imposed on them. One year later, this author then undertook in the Anatomical Laboratory of Cornell University Medical College, New York City, the problem of the conditions that allowed these cells to grow in the cultures. The medium chosen for this study was plasma prepared from the blood of healthy animals. The plasma was selected as medium because it represented a normal fluid existing everywhere in the normal organism. There was no evidence to show that cancer developed necessarily in an abnormal organism. In fact, transplanted cancer fragments grow best in young, healthy animals.

This study showed that in plasma this active independent growth of cells depends on three factors: (1) an ample supply of oxygen (which is about one third of the oxygen concentration of the air [28]); (2) a crowding together of the cells in a minimum amount of medium, and (3) a stagnation of this medium. These factors applied not only for the *growth of normal cells, but also for the growth of cancer cells in vitro* (animal and human cancer, carcinomas and sarcomas).[29]

Single cells carefully washed of tissue juices will not grow and often fail to show any reaction whatsoever when placed in a layer of pure plasma diluted with salt solution. On the other hand, if a salt solution extract of any actively growing tissue is added to the plasma, then single cells show immediate activity. They migrate, take up fats and proteins, digest these substances, grow actively and divide by mitosis.

In pure plasma, such an active growth will take place only about fragments of tissue. About these fragments, it is proportional to the age of the tissue, to the size of the fragment and cell density of the fragment and inversely proportional to the thickness of the layer of medium or the amount of absorbing medium about the cells. These proportions in relation to the size of the fragment and the thickness of the layer of medium hold only within limits of active diffusion of oxygen. These diffusion limits were measured and found to be from 1 to 2 mm. for most tissue fragments and from 0.5 to 0.7 mm. for clotted plasma or serum. About fragments of tissue larger than from 1 to 2 mm. in diameter, the growth is inhibited by a lack of oxygen to their central parts and toxic products liberated by the autolysis that results. Definite abnormal reactions are noted in cells in the deeper parts of layers of plasma thicker than 0.5 to 0.7 mm.

The relation of the size of the fragments and the thickness of the layer of medium was studied in fragments of tissue ranging from

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28. Burrows, M. T.: The Oxygen Pressure Necessary for Tissue Activity, Am. J. Physiol. **43**:13 (April) 1917.

29. Burrows, M. T.: The Tissue Culture as a Physiological Method, Tr. Cong. Am. Phys. & Surg. **9**:77, 1913; Tissue Culture in Vitro, Tr. XVII Internat. Cong. Med., Gen. Path. and Path. Anat., London, p. 217, 1913; The Cultivation of Human Cancer Cells in Vitro, M. Rec. **86**:649, 1914.

1 mm. in diameter to a single cell, and in layers of plasma ranging from 0.2 to 0.7 mm. in thickness. In this study it was noted that while growth will obtain about fragments of a given tissue 1 mm. in diameter in a layer of medium 0.5 mm. thick, it will fail about a 0.5 mm. thick fragment of the same tissue in the same thickness of the layer of medium, but succeed about this smaller fragment (0.5 mm. thick fragment) in a thinner layer of plasma medium, 0.25 mm. thick.

Under these conditions of the proper thickness of the layer of medium and the proper size and cell density of the fragment, it is interesting to note that growth does not begin at once, but always after a given latent period. This latent period is shortest about the cellular fragment of actively growing tissues of young embryos and cancer. It increases in length about similar fragments of older and older embryos and is longest about the less cellular, nongrowing fragments of the adult.

As shown in another article [23] this difference in the latent period is not related to the age of the tissue in these cases, but to their immediate growth rate. It is much shorter for the cells of a piece of growing granulation tissue than for those of the normal connective tissue and shorter for the cells of an actively growing cancer than for those of a slower growing one.

It must be pointed out here that not only the growth of the cells is dependent on a proper supply of oxygen, stagnation, cell crowding and a proper minimum amount of medium, but all activity in these cells is dependent on these conditions. The cells in a cellular fragment of tissue first show migration, then growth and finally a complete disintegration or self-digestion.[30]. These various changes take place in regular sequence. Growth is only one phase of a general change induced in them by their environmental surrounding in the culture. Each of these changes begins in the cells of the center of the fragment. It then spreads from this point to involve more and more of the cells toward the periphery. The cells in a 1 mm. thick fragment of mesenchyme of a young embryo placed in a layer of plasma 0.5 mm. thick show all of these changes. As one decreases the size of such fragments, leaving other conditions unchanged, the amount of each of these changes not only decreases, but they begin to disappear in the reverse order in which they appeared about the larger fragments. In a culture of a medium size fragment self-digestion disappears except in the cells in the center of the fragment and growth becomes very limited. In still smaller fragments migration alone is observed. The cells in the latter cases do

30. This digestion of cells has been called self-digestion to distinguish it from autolysis. It is a digestion that takes place in the presence of oxygen and does not liberate toxic products. Autolysis, as the word is used, is a digestion taking place in the absence of oxygen. Toxic products are liberated in the autolysis of cells.

not disintegrate, but after becoming sufficiently separated they come to a state of complete inactivity. In this state they remain intact but inactive until destroyed by outside means. The cells in fragments of mesenchyme of older embryos and of the connective tissue of adults behave in the same manner. The cells in the sparsely cellular fragments show only migration and then inactivity. In the more cellular fragments growth and self-digestion intervene in proportion to the cell density of the fragments. The chief difference between these fragments of the older tissues and the more actively growing ones is that these changes take place after a much longer latent period.

From these observations it became evident that the life of these cells is something that is determined by their immediate surroundings. It is the result of a reaction between them and their environment. It has been taught that body cells are continuously active. Bayliss points out that there is no evidence for this view.[31]

These cells which had migrated from the fragment and come to rest apparently disproved it. Several such cultures have been kept in the presence of an ample supply of oxygen and in the incubator for as long as six months. After fourteen days the cells became inactive and remained so for the remainder of this entire period. They showed no changes in shape nor changes in their protoplasm. The fat droplets and others contained bodies that remained undisturbed in them during this time. At the end of this period these cells were found able to become active again. They migrated and grew when placed in drops of fresh plasma.[32]

The picture of life in these cells isolated from the body assumes, therefore, proportions of much greater simplicity than had been generally suspected from a study of them in the body. While previous students [33] of regeneration had appreciated that growth is regulated by factors other than food and oxygen, the nature of these other factors and their significance seemed impossible until we had found a method for isolating these cells and studying them under known and controllable conditions. Summing up the foregoing conditions necessary for their cellular activity in the culture, it became evident that they may signify that activity in these cells is dependent on the accumulation of some substance or substances formed by the cells but also readily diffusible into plasma. They also indicate that migration, growth and self-digestion may be merely the result of different concentrations of this substance or substances. Cells showing only migration and then complete inactivity had been seen only in culture of the more sparsely cellular fragments of tissue of older embryos and adults. Growth and

31. Bayliss, W. M.: The Principles of General Physiology, London, 1915.
32. Burrows: (Footnote 29, second reference, Fig. 4).
33. Morgan, T. H.: The Physiology of Regeneration, J. Exper. Zool. **3**:457, 1906.

self-digestion are peculiar to the more cellular fragments of embryonic mesenchyme and cancer. When a large number of cells are crowded into a small amount of medium, all phenomena proceed. When few cells are placed in a relatively large amount of medium, the cells may become inactive after showing only migration.

An attempt was made, therefore, to ascertain whether such a substance or substances accumulated in these tissues during the latent period and accounted for the activities noted in the cells. Fresh fragments of actively growing tissue of embryos and cancer and slower growing tissues of older embryos and adults were extracted with an equal weight of isotonic sodium chlorid solution, and the extracts tested by placing equal parts with equal parts of plasma. The mixture was used as medium for isolated embryonic heart muscle and mesenchyme cells. Fragments of the same tissue left in a culture for from forty-eight to 128 hours were also extracted and the extracts tested in the same manner. In the presence of the extracts of the fresh tissues of the older embryos and adults, the isolated cells suffered little or no change, while the extracts of similar fragments left in the stagnant cultures for several days stimulated an active migration, growth and in some instances self-digestion in these isolated cells. Extracts of fresh tissue of the younger embryos and cancer stimulated immediate activity in these cells.

The cells of the more inactively growing tissues lying in the stagnant culture had evidently accumulated a definitely active substance. Extracts containing this active substance, $S$, were then carefully studied. In low dilutions ($S^1$), they were found to have no effect. In medium concentrations ($S^2$), they stimulated the cells to migrate and engorge themselves with particles of proteins and fat droplets. In high concentrations ($S^3$), these cells digested these proteins and fats, grew actively and divided by mitosis. In all higher concentrations ($S^4$), the cells suffered a self-digestion.

The picture of migration followed by growth and then self-digestion was only the result of a gradual accumulation of the $S$ in the stagnant layers of plasma. A few cells had failed to grow in the thicker layers of medium because the proper concentration of the $S$ could not be formed and retained by them. It is soluble in the salt solution and diffuses away into the plasmatic medium. A few cells cannot supply a large enough quantity of this substance to raise its concentration to the growing point in a large bulk of medium. About the less cellular fragments placed in a relatively large bulk of medium, the cells come quickly to rest because the diffusing $S$ comes quickly to a concentration too little for any kind of cell activity. The cells cannot retain this substance. Its concentration is determined not only by the amount formed by the cells but also by the amount removed by the medium.

On account of these facts this substance or substances, *S*, has been named the *archusia,* the driving substance of the cell. It is evidently the energy for life in the cell. In studying its formation it was found that it is formed only in the presence of oxygen and certain food materials, not determined, but easily exhausted from a drop of plasma and renewed by adding fresh plasma or serum. Again, it was noticed that when it is present in the medium, the cells will react normally without oxygen until it is exhausted. They then suffer autolysis.[34] It is the only substance in the cell whose formation demands oxygen. In its presence digestion and synthesis proceed without oxygen.

The condition necessary for growth in the body cells is probably not different, therefore, from that noted by Wildiers for yeast. Single yeast cells will not grow in a large bulk of medium unless an extract of yeast is added, while a number of yeast cells added to the same quantity of medium begin to grow very actively after a latent period. Wildiers noted that this failure for the single cell to grow is due to the absence of a substance, *bios,* which is contained in the extracts of yeast and appears in the wine casks when a sufficient number of yeast cells are added.[35]

In the more careful analysis of this phenomenon discovered in body cells, the active substance, the archusia (*S*), has been found to be formed by the oxidation of food substances by the cell and shown to act to produce the manifestations of life in the cell, and to act according to its concentration to produce these different manifestations. It is evidently comparable, therefore, to the heat in the steam engine. The heat acts in the engine to produce work in proportion to its concentration. The archusia differs from the heat only in that it induces chemical changes in the cell rather than purely physical ones.

In the engine, it is well known that the work performed is as much dependent on the heat conserved for the water as the heat produced in the fire box. Take off the heat jacket of the boiler so that the heat may escape to the outside, the engine stops. It is interesting to note that the same holds for the cells. The body cell has lost or has failed to develop means to retain its energy, the archusia. This escapes from it or is not formed by it except when it is placed in a stagnant environment rich in food and oxygen, and in association with other cells also forming it. In recent years a great amount of study has been devoted to determining the amount of oxygen adsorbed in the body and the carbon dioxid and water eliminated. It is interesting that these studies have yielded little of immediate practical importance. From the

34. Burrows, M. T.: The Reserve Energy of Actively Growing Embryonic Tissues, Proc. Soc. Exper. Biol. & Med. **18**:133, 1921.

35. Wildiers, E.: Nouvelle substance indispensible au developments de la levure, La Cellule **18**:311, 1901.

studies cited above, it becomes evident that the activity of the body is not alone dependent on the energy produced but also on the energy conserved.

### FUNCTION AND DEVELOPMENT OF DIFFERENT TYPES OF CELLS OF BODY

In the first cultures of chick embryos, active rhythmic contraction of the heart muscle cells was also observed in the fragments and whole hearts transplanted to the cultures.[27] It was interesting to note that these heart muscle cells which had been contracting in the fragment lost this ability to contract as they migrated from the fragment into the medium of most cultures. In the medium they assumed the shape, grew and divided like simple mesenchyme or sarcoma cells. It became evident, therefore, at this early time that whether these cells are to grow, divide and invade the medium or contract rhythmically depends probably on their immediate surroundings.[36] In these cultures of embryonic tissue, it was interesting to note, however, that their tendency was to revert from a functional to a growing state. Only the cells in the more central regions of the fragments continued to contract, while those in the periphery stopped this act and invaded the medium as fast as the cells outside them moved away.

The cells in fragments of embryonic striated muscle from the limbs and back also contract rhythmically in the cultures. The contractions are exactly like those of the heart muscle. These muscle cells in contact with the medium also quickly revert to cells indistinguishable from the simple mesenchyme or sarcoma cells. Under proper conditions they may grow actively and divide by mitosis, or they may migrate as long spindle shaped cells or spread from the tissue as an open syncytial network.

While in the great majority of cultures, there is no tendency for these cells which migrate from the fragment to revert and develop function again, in an article[37] published in 1912, one cell and an open syncytium were noted to undergo this change. Since that time eight more such isolated contracting cells and contracting syncytia of cells have been observed in eight cultures out of several thousand studied with this and other ends in view. These cells when cut from the circulation of the body and placed in the stagnant culture accumulate archusia about them and thus tend always to revert to a state of growth rather than function.

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36: Burrows, M. T.: An Attempted Analysis of Growth, Anat. Rec. **9**, Paper 11, 1915; The Tissue Culture in Cancer, Tr. Second Pan. Am. Sc. Cong., Washington, Section 8, Part 2, p. 494, 1915.

37. Burrows, M. T.: Rhythmische Kontraktionen der isolierten Hertzmuskelzelle ausserhalb des Organismus, München. med. Wchnschr., No. 27, p. 1, 1912; Science **36**:90, 1912.

In the cultures where one places a fragment of embryonic muscle tissue from 0.5 to 1 mm. thick, the central parts of these fragments suffer a self-digestion [38] from an overabundance of the archusia. A liquid substance is liberated by this digestion. This liquid flows out over the surface of the layer of medium to form a tough film. This film is not only rich in food material but also in archusia. The heart muscle cells entering it flatten out to take an otherwise spindle or irregular shape, grow actively and divide by mitosis. The fragment is also rich in accumulated archusia at this state.[23]

Noting the latter facts, it had become of interest to see if the environment played any rôle in determining this rhythm in such isolated rhythmically contracting cells. While it is true that much has been written about the mechanism of muscular contraction, nothing is known except certain isolated facts:

1. Berstein noted several years ago that the energy of muscular contraction has a negative rather than a positive temperature coefficient. Only surface energy can have a negative coefficient in muscle.

2. Fletcher and Hopkins had noted that lactic acid is liberated at the contraction phase and that oxygen is absorbed only during relaxation.

3. Electrical responses to contraction and the heat changes in muscle have also been carefully measured.

It was interesting in observing these contracting heart muscle cells to note that they occupied a peculiar position in the medium. They were not at the surface of the medium nor in the clot but stretched through a serum cavity between the fragment or the surface film and the ends of the bands of fibrin. One end of these cells was in contact with an area rich in archusia; the other end was in contact with bands of fibrin extending into the open medium. In this medium the archusia diffuses readily. This end in contact with the fibrin must have a very low archusia value.

These cells had gained this position through adhering to the clot, which had loosened from other parts of the side of the fragment and contracted away from it. They had thus become stretched between the fragment and the clot. In other cultures isolated cells were dragged out by the same means so that they became stretched between the surface film and the ends of fibrin fibrilli in the clot.

In studying the action of archusia on the cells, it was found that it acts to liberate another substance, the *ergusia*. This substance decreases the surface tension of cells. Such a decrease in surface tension is associated with electrical changes. This decrease in surface tension causes the

38. Burrows, M. T.; Burns, J. E., and Suzuki, Y.: Studies on the Growth of Cells: The Cultivation of Bladder and Prostatic Tumors Outside the Body, J. Urol. **1**:3 (Feb.) 1917.

cell to stretch in the direction of its lowest surface tension. In these cells this decrease in surface tension can take place only at the end of the cell in contact with the fragment or the surface film. Under the influence of this decrease in surface tension at one end, these cells must suffer one of three kind of changes: (1) a breaking loose from the fibrin; (2) a tearing of the cell in the middle, or (3) a breaking down of the surface tension lowering substance or the substance that adsorbs it. In the great majority of cultures in which fibrin contracts as described above, the cell quickly breaks loose from the clot. None of them break in the middle. In a few out of the several thousand rhythmicity resulted. These cells contract as the result of a periodic reduction in their surface tension followed in each instance by a breakdown of this surface tension lowering substance or the substance adsorbing it. Lactic acid is liberated. Lactic acid increases the surface tension of the cell or makes it shorten. The ergusia reforming decreases the surface tension or makes the cell lengthen. Such a breakdown is associated with an electric current passing from one end of the cell to the other. It will result always when any simple system like these cells is polarized as the contracting heart muscle cells were found to be polarized.[39]

On several occasions such contracting cells were removed from this position to the serum. In the serum they became spherical in shape and inactive. The same cells removed to the surface film stretch out to take a flattened spindle or irregular shape, grow and divide and look like sarcoma cells. Others were placed in the fibrin outside. They remained inactive or stretched out along the fibrin fibrilli and became inactive.[36]

It was thus possible to show absolutely that function and growth in these heart muscle cells are determined by the environment and not by the cell. They are reversible phenomena. The change of a cell from the state of active function in the normal organism to the growth observed in cancer must be a normal reaction of the cell to a changing environment. Ribbert's contention had thus been realized.

While it was thus possible by means of the tissue culture to transform a functioning cell to a growing cell and vice versa, it has not been possible to transform a connective tissue cell into a muscle cell or an epithelial cell into any other type of cell. These cell types are determined by some stable internal mechanism in the cell. This fact one might have readily deduced from the study of cancer, however. There is no evidence that a cancer cell is other than the growing connective tissue or epithelial cell from which it arose. Teratomas develop only from egg cells. The egg cell can give rise only to multiple cell types. A

39. Burrows, M. T.: A Note on the Mechanism of Heart Muscle Contraction, Am. J. Physiol. **45**:556, 1917.

growing smooth muscle or striated muscle cell resembles growing connective tissue cells.

There is no evidence, as many recent authors have attempted to show, that the cancer cell is a specially differentiated cell, nor is there any evidence in the whole of embryology or experimental biology that such a cell may arise. On the other hand, it can be fully proved by the tissue culture that any cell may grow if given the proper surroundings and this growth may be independent. These surroundings are simply those which allow a certain high concentration of their archusia to accumulate about them. This archusia may be supplied from without or by the cells themselves when they are crowded into sufficiently narrow stagnant confines. Under the latter conditions, the growth of body cells becomes wholly independent. This is cancer. When supplied from other sources, their growth becomes dependent on the supply.

Function on the other hand comes into existence when the cell is so placed that the archusia remains in concentration only at one end. The type of function is determined by the more fundamental constitution of the cells in question. Connective tissue cells and epithelial cells stretched as the heart and striated muscle cells were stretched (described above), do not contract rhythmically. Smooth muscle cells so stretched contract rhythmically, but their contractions are not like the heart muscle and striated muscle cells, short and rapid, but are slow. They are exactly like the contraction peculiar to smooth muscle in the body.

In the body all functional cells have this arrangement. The nerve fibers are stretched between the dense brain tissue and an end organ. The gland cells are in contact with an active blood circulation on one side and a stagnant gland tube on the other. The archusia is washed away by the blood stream from their outer ends and accumulates at their inner ends. Functioning glands and nerves show electrical changes as muscle shows these changes.[31] While their function is different from that of the muscle cell, it is determined by the same organization and is evidently the result of an explosive breakdown of a polarized system. It differs from the muscle because of a different physical chemical make-up in the epithelial and other cells.

In the culture function had been forced on the heart muscle cells through a contraction of the clot away from the fragment. In the body the cells are forced to function through the development of intercellular tissue and blood vessels. In further proof for these deductions, it is noted that epithelial cells from glands of the body revert in the cultures to broad sheets of migrating and growing cells. Champy [40] found that if connective tissue is added to such culture the epithelial

40. Champy, C.: La presence d'un tissue antagoniste maintient la differentiation d'un tissu cultive en debois de l'organisme (Note preliminaire), Comp. rend. Soc. de biol. **76**:30, 1914.

cells are forced to form tubular structures again. Drew [41] has confirmed these observations of Champy.

### CONDITIONS REGULATING GROWTH IN THE BODY

In the light of these facts, growth and function in the body take on quite different aspects. Function is something peculiar to an active circulation in properly arranged blood vessels. Growth is something peculiar to stagnant crowded cell areas where the circulation is poor. In this regard body cells are not different from any of the simple unicellular organisms. It is in the stagnant pool and not in the running stream that such life abounds. Wildiers had found that the growth of yeast depends on conditions identical with those outlined above for the growth of body cells. In 1923 experiments with a culture chamber which allowed the tissue to be washed continuously with a stream of serum were described. In these experiments it was found that washing prevents the growth of heart muscle cells but accelerates and makes their rhythmical contractions regular and forcible.[42]

In the development of the animal body, it is interesting to note that growth is most active at the beginning. It wanes and is replaced by function as the blood vascular system develops. At maturity growth ceases except as it is necessary for repair, regeneration and in certain parts, such as, the nails, hair, sex glands and bone marrow.

Areas undergoing repair and various of the more permanently growing regions and cancerous tissues have been studied. In the wound, growth does not intervene alone at its edge but throughout the wide area of tissue behind its edge, which is suffering from the inflammatory slowing of the circulation. This growth behind the edge of the wound is proportional to the amount of congestion and slowing of the circulation. In the wound the greatest growth takes place in the stagnant wound areas where the blood vessels have been completely destroyed.[43]

The distal end of the growing nail bed has a greatly reduced circulation. This area is supplied by a single layer of large sinusoids. These sinusoids are larger than the vessels which fill and empty them. The bone marrow has the same sluggish sinusoidal circulation. The growth in the sex gland is inside the tubules and follicles far removed from the blood vessels. Cancer is a densely cellular tissue supplied by irregular tortuous vessels few in number per unit cell area or by large dilated

41. Drew, A. H.: Growth and Differentiation in Tissue Cultures, Brit. J. Exper. Path. **4**:46 (April) 1923.

42. Burrows, M. T.: Studies on Cancer, 4 papers, Proc. Soc. Exper. Biol. & Med. **21**:94, 1923.

43. Burrows, M. T.: Studies on Wound Healing: I, "First Intention" Healing of Open Wounds and the Nature of the Growth Stimulus in the Wound and Cancer, J. M. Res. **44**:615 (Sept.) 1924.

sinusoids. These vessels are being continuously destroyed in its more central parts. Hemorrhage and necrosis are the result.[44]

In the light of these facts it became evident, therefore, that cancer may be nothing more than the result of any substance or condition that can primarily build in the organism a dense mass of cells having a relatively poor blood supply. Cancer is only such a tissue organization. It is not a primary change in the cell.

The proof for this deduction lay in showing that such an organization once induced can reproduce itself and destroy the organism and that the substance or conditions, such as coal tar, which induce it, act only to produce such an organization.

In a previous article,[43] one of us has already discussed and given proof that such an organization once established preys on and destroys the surrounding less crowded and more vascular normal tissue. All these normally arranged cells are attacked alike, including the endothelial cells of the blood vessels. A mass of cells thus sufficiently crowded and stagnant not only reproduces itself through a growth of its cells but also the environment suitable for a continuation of this growth by its continuous destruction of its own vascular supply and that of the tissues about it. This destruction of the blood vessels is greatest in the tumor. The central parts of these tumors suffer necrosis. The peripheral parts receiving sufficient oxygen continue to grow actively.

This attaching of a less dense mass of cells by another denser mass was first noted in a study of the behavior of fragments of normal skin of embryos of various ages in the cultures. In the early embryonic life, the epidermis is a single or a double layer of cells. The underlying connective tissue or mesenchyme is a densely cellular layer. As development proceeds in the embryo, the epidermis gradually becomes a thick cellular layer while the mesenchyme cells cease to multiply at an early time. This layer expands rather by the laying down of intercellular substances, the connective tissue fibrils. When this laying down of fibrils between the mesenchyme cells takes place, they become widely separated so that the number of cells per unit area in this layer becomes only a fraction of their original value. When fragments of the skin of the younger embryos are cut from their circulation and placed in the cultures, the mesenchyme cells grow most actively and destroy and devour the protoplasm of the cells of the less cellular epithelial layer. About fragments of older and older embryos, the activity of the mesenchyme wanes in the cultures and the epithelial layer becomes more and more active to dominate completely about the fragments of older

44. Burrows (Footnotes 13, 42 and 43): Factors Regulating Cellular Growth and Their Importance in the Explanation of Cancer, South. M. J. **17**:233 (April) 1924.

embryos, as the mesenchyme had dominated in the earlier period. These active epithelial cells then destroy the cells in the less densely cellular connective tissue area. This growth of densely cellular layers can be greatly facilitated by adding embryonic extracts to the plasma.

Epithelial cells, as Fischer [45] has shown, do not grow readily in the cultures unless these embryonic extracts are added to the medium. Barta [46] has carefully studied the behavior of epithelial cells in fragments of the ureter of young rats. The ureters of rats are small. One millimeter fragments of the whole cross section can thus be placed in the culture without destroying the oxygen supply to all parts of this fragment. In a medium containing embryonic extracts, he found that the epithelial cells grew actively to invade the connective tissue and fat of the adventitia in a manner typical of true cancer. These growing cells reduced the muscle, blood vessels and connective tissue to a hyaline mass and destroyed the fat tissue. Their invading epithelial cells contained mitoses, irregular, large multinuclear cells, and were in every way identical with cancer.[46]

Maximow has found the same phenomena in fragments of breast planted in a medium containing extracts of bone marrow.[47] Burrows had noted a sarcomatous overgrowth of the mesenchyme in embryonic fragments placed in pure plasma and the phenomena greatly exaggerated in a culture of these tissues into which an extract of embryos or cancer tissue is added. A few of these fragments transplanted into the subcutaneous tissue of an adult rat developed into true sarcoma.[48]

Burrows has also found that this dominance of a more cellular and less vascular layer over a more vascular and less cellular layer occurs in wounds as well as in the tissue culture and in cancers. When the wound is open and suffering a congestion and slowing of its circulation, the granulation tissue grows actively in areas removed from the originally more densely cellular epidermis. As the epidermis moves in over the wound and the circulation is reestablished in the granulating area, growth ceases in this area, but continues in the more densely cellular epithelial layer until the granulations are reduced to a hyaline mass. The cells and blood vessels are destroyed by this growth of the epithelial layer, which continues until its blood supply is thus reduced and atrophy intervenes.[43]

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45. Fischer, Albert: A Three Months Old Strain of Epithelium, J. Exper. Med. **35**:367 (March) 1922.

46. Barta, E.: Experimental Histological Studies, I, Some Factors Regulating the Morphology of Tissue (Ureter in Vitro), Anat. Rec. **29**:33, 1924.

47. Maximow, A.: Tissue Culture of Mammary Gland, Anat. Rec. **27**:210, 1924.

48. Burrows, M. T.: The Experimental Production of Malignant Ulcers in Rats, J. Missouri State M. A. **20**:145, 1923.

Such scars may become the site of cancers. It has also been found that the failure for the wound to become cancerous in every case is due to the fact that the epithelial layer under ordinary conditions does not become thick enough to overpower the resistance of the body outside. If this layer is stimulated to increase in thickness through the addition of growth stimulating substances to it, cancer may then intervene."

### THE ACTION OF COAL TAR AND OTHER LIPOID SOLVENTS IN THE PRODUCTION OF CANCER

Before attempting an investigation of the action of coal tar and other lipoid substances in the production of cancer, it seemed necessary first to study more carefully the general metabolism of fat by body cells. While many authors had studied the heat produced in fat metabolism and the various by-products into which fat may be changed, no analysis of the ingestion of fat and fat bodies by the cell had been undertaken.

In the early part of this article it has been shown that under the influence of a medium concentration of the archusia ($S_2$) the cell takes up fat, but does not digest it. Under the influence of higher concentrations of the archusia ($S_3$), the fat and proteins so taken up are digested and growth intervenes. How this fat is taken into the cell was then investigated by the senior author.

In this analysis it was noted that body cells, unlike many of the unicellular organisms, have no distinct mechanism for migration. They are simple fluids. They can migrate only into substances containing fats and proteins which have greater inertia than themselves. If the fats and proteins are in suspension and are mobile, they are drawn to the cells. If these same substances are fixed or large and have a greater inertia than the cell, the cells are drawn to them. The mechanism for migration in body cells is the mechanism for taking these necessary food substances into themselves. Migration is merely an adaptation of the growth reaction of these cells as function is an adaptation of the same reaction. These cells migrate or draw food into themselves by liberating a substance that has strong affinities for the cell as well as proteins and fat of the medium. This substance or substances has been named the *ergusia*, the laboring substance of the cell to distinguish it from the *archusia*, the driving substance of the cell.

In the plasma cultures the cells do not liberate the ergusia under all conditions, but only when the archusia accumulates to a certain concentration ($S_2$), as has been pointed out above. In the presence of this concentration of the archusia, the cell liberates the ergusia [49] which is adsorbed by the clot and fat in the clot. If the clot is held firmly through attachments to the glass surface on which it is placed, the cells are drawn out into it and the fragments spread and flatten out. If the

49. Credit for the words archusia and ergusia is due to Prof. Thomas S. Duncan of the departments of Greek and Latin, Washington University, St. Louis.

clot is not attached, it is drawn in mass to the fragment. In the same manner, small, mobile fat droplets are drawn into the cell. Larger, less mobile masses of fats draw the cells to them.

In studying the ergusia in the different types of cells it is interesting to note that it differs in different cells. It has only one definite common property: it is adsorbed readily only by proteins and fats. The ergusia of the connective tissue coagulates blood to fibrin and serum. The ergusia of the epithelial cells has the same property, but these cells differ from the connective tissue cells in that they may later dissolve the fibrin formed. The ergusia of the leukocytes and lymphocytes does not form fibrin to any great extent. Their ergusia is readily adsorbed, however, by both the fibrinogen and fats.

In proof that the cells migrate and acquire their food by this means, it was not only found that their movements are often unassociated with any changes in their contour (they migrate without ameboid movements) or evidence of other mechanical mechanisms, but also that they are exactly proportional to the liberation of this substance as such liberation is identified by the action of the ergusia of the connective tissue and epithelial cells on a plasma clot, and through the proof that the fat taken up by the cells becomes saturated with this ergusia.[23]

In a short time after fats are eaten by animals their blood contains a large amount of this fat. It occurs in the blood in the form of suspended droplets. The plasma, prepared from such blood, is rich in fat. If a fragment of connective tissue is placed in a drop of this plasma, the cells become filled with these fat droplets. The fat moves rapidly out of the plasma into the cells. The fat has no coagulating effect on the clot. It prevents its coagulation rather than stimulates it. This fat after it is taken up by the cells acts differently. If the fat droplets are squeezed from these cells and placed in fresh plasma, they coagulate the plasma, stick to the fibrin fibrils thus formed and assume spindle shape quite the same as the connective tissue cells. When placed near other connective tissue cells, they repel these cells or are repelled and driven away from the cell exactly as one connective tissue cell repels another in the culture. These last phenomena continue, however, only until the ergusia which they have adsorbed is lost to the clot. Then they are adsorbed again by the cells when brought in contact with them.

In other experiments, it was found that this taking up of the ergusia follows the laws of adsorption or solution. There is a definite saturation point for ergusia in proteins and fats. These cells can migrate into these substances or draw them into themselves only until the concentration of the ergusia in the particles is balanced with that in the cell. Then all activity ceases.[36]

In the light of these experiments, it became evident, therefore, that if one places in the tissue any viscid, more or less immobile and non-

digestible substance that has strong affinities for the ergusia it must draw the surrounding cells to it and away from their intercellular substances and blood vessels. It can thus disrupt the normal tissue organization up to the time it becomes saturated with this substance. This action accumulates the scattered cells of the tissue in dense stagnant masses about the absorbent and thus builds an organization in which the cells can accumulate their archusia and grow. It builds a nonvascular cancerous organization.

### ACTION OF COAL TAR

Having established these facts, Jorstad [50] in this laboratory then undertook the study of the action of coal tar in the production of cancer. Jorstad injected small quantities, from 1 to a few cubic centimeters, of crude coal tar into the subcutaneous tissue of rats and also into embryonic tissue that had been cut into small fragments and injected under the skin of animals. These masses of coal tar were in some cases left for a long time and then removed. Others were removed at regular intervals of twenty-four hours and longer. In a few instances the coal tar was injected just beneath the epidermis so that the reaction of the epithelial cells could also be observed. In most instances it was injected into the subcutaneous tissue far removed from the epithelial layer.

The change induced by the drops of tar is a rapid migration of the cells of the tissue to their edges. In a few cases the tar broke up into a number of smaller drops. In most cases, however, it remained together as one large drop. These cells accumulating from wide areas in the tissue formed a collar around the drops of tar. The first cells to react to the drop underwent a granular degeneration in most of the experiments. The later cells remained intact. The cells chiefly attracted were the connective tissue cells and the endothelial cells of the capillaries. The capillaries themselves, therefore, disappeared through this movement and separation of their endothelial lining cells. The intercellular materials were little disturbed except that they showed a hyalin-like degeneration and became stripped of the fibroblasts, which normally lie scattered among them.

The action of the single drop of coal tar was limited in this capacity. Its action was most rapid at first. Then this activity ceased slowly, to stop in the course of a few days, as any substance that dissolves substances from a medium ceases as the distribution constant is satisfied between it and the medium.

In the sparsely cellular subcutaneous tissue, but few cells were thus collected by a single drop of coal tar. In the more cellular mesenchyme of embryos, the tar accumulated many more cells. This was also true

50. Jorstad, L. H.: A Study of the Behavior of Coal Tar on the Tissue, Proc. Soc. Exper. Biol. & Med. **21**:67, 1923; The Behavior of Coal Tar in Embryonic and Adult Tissues, J. Cancer Res., to be published.

when the tar was placed in contact with the more densely cellular epithelial layer. In the adult connective tissue, growth was never observed in the cells collected by the tar. In the more cellular mesenchyme of embryos in which a greater number of cells were collected, these masses became larger and more densely cellular. In these larger masses growth and division figures were seen. Against the epithelial layer of the skin the tar collects more cells, and in these denser masses of epithelial cells growth and division figures are always seen. This growth often leads to the formation of pearls and the picture of precancerous lesions. In the epithelial layer of embryonic tissues, typical cancerous lesions made their appearance.

The action of a single drop of coal tar is limited. It does not act to stimulate the cells to grow but only to draw them to it and accumulate them in dense masses about it. If these cell masses become sufficiently dense and large enough, growth may then later intervene as the archusia of these cells accumulates about them. To produce such large masses many applications of tar are generally necessary. With a single injection this is never accomplished in the animal under ordinary conditions. The cells collected soon suffer regression and hyaline changes, therefore. Eventually a hyaline scar surrounds the drops of tar. In a few instances after a time the drops of tar saturated with ergusia begin to migrate. They enter the veins and migrate to distant organs in the same manner as fat droplets squeezed from body cells migrate from fragments or other cells into the less saturated parts of the medium of the culture. The blood contains little or none of the ergusia peculiar to the fixed tissue cells. It acts as a solvent for this substance and attracts the tar.

These observations indicate, therefore, that the action of coal tar is not chemical, but purely physical. It acts merely by dissolving a lipoid soluble substance of the cells. It is possible that in the fractional distillation of coal tar one will find a substance having a more efficient solvent action, but it is not likely that any important growth stimulating substances will be found, as many of the English authors have supposed. Any oil having a similar solvent action must act accordingly.

### ACTION OF PARAFFIN AND PARAFFIN OILS

To prove the latter deductions more definitely, it became of interest to see how other oils act in this regard. Previous studies have shown that paraffin and paraffin oil applied frequently to a point on the skin will induce cancerous growths, as coal tar induces them. Mook and Wander [51] noted that single injections of paraffin into the subcutaneous tissue of men lead to the production of tumors. They

51. Mook, W. H., and Wander, W. S.: Camphor Oil Tumors, Arch. Dermat. & Syph. **1**:304 (March) 1920.

found these tumors composed of drops of the oil enclosed in a hyaline, fibrous capsule. These tumors are similar, therefore, to the tumors that Jorstad found in animals injected with single drops of coal tar.

The paraffin in the cases studied by Mook and Wander had been injected into patients as a vehicle for camphor and other drugs. This discovery that this oil forms tumors led to the discontinuing of its use as a vehicle and the substitution of Mazola, or corn oil.

It is well known that corn oil has no immediate food value other than the fat it contains. It is largely free from vitamin. One of us (C. G. J.), in performing experiments with the Allen-Doisy hormone,[52] noted that this oil also produces tumors. The Allen-Doisy hormone was dissolved in this oil and given hypodermically. It thus became of interest for us to study the action of pure corn oil when injected into the subcutaneous tissue. Previous authors had noted that many oils of the food when injected subcutaneously are not absorbed, but no one had studied the action of these oils on the tissues.[53]

### THE ACTION OF MAZOLA, OR CORN OIL

Thirty-nine rats, one monkey and one dog were used for these experiments. From 1 to 5 c.c. of the pure sterile corn oil was injected into the subcutaneous tissue of each animal. The oil was injected in each instance so that it formed one large oil droplet. This mass broke up quickly into numerous drops of various sizes. These drops remained unabsorbed. Each drop then became firmly encapsulated so that a multiple cystic tumor was formed, similar in each case to the one removed and photographed (Fig. 1). The nature of the changes that this oil induces in the tissue was studied by removing such tumors at regular intervals of one, two, three and one-half and seven days, after two and four weeks, and after two, three, five and seven months.

### PROTOCOLS

EXPERIMENT 1.—Two cubic centimeters of sterile Mazola oil was injected into the subcutaneous tissue of four rats. After twenty-four hours the oil tumors were removed. They consisted of a large number of small and larger cysts each enclosed in a grayish capsule, which varied from 1 to 3 mm. in thickness. One of these tumors was fixed in formaldehyd, the other three were fixed in Zenker's fluid; a part of the formaldehyd fixed tissue was cut with the freezing microtome and stained for fat. Other parts and the Zenker fixed tissue were dehydrated, embedded in paraffin, sectioned and stained with hematoxylin and

52. Allen, Edgar; Francis, B. F.; Robertson, L. L.; Colgate, C. E.; Johnston, C. G.; Doisy, E. A.; Kountz, W. B., and Gibson, H. V.: The Hormone of the Ovarian Follicle; Its Localization and Action in Test Animals, and Additional Points Bearing upon the Internal Secretion of the Ovary, Am. J. Anat. **34**:133 (Sept.) 1924; The Extraction and Some Properties of an Ovarian Hormone, J. Biol. Chem. **61**:711 (Oct.) 1924.

53. Henderson, Yandell; and Crofutt, E. F.: Observations on the Fate of Oils Injected Subcutaneously, Am. J. Physiol. **14**:193, 1905.

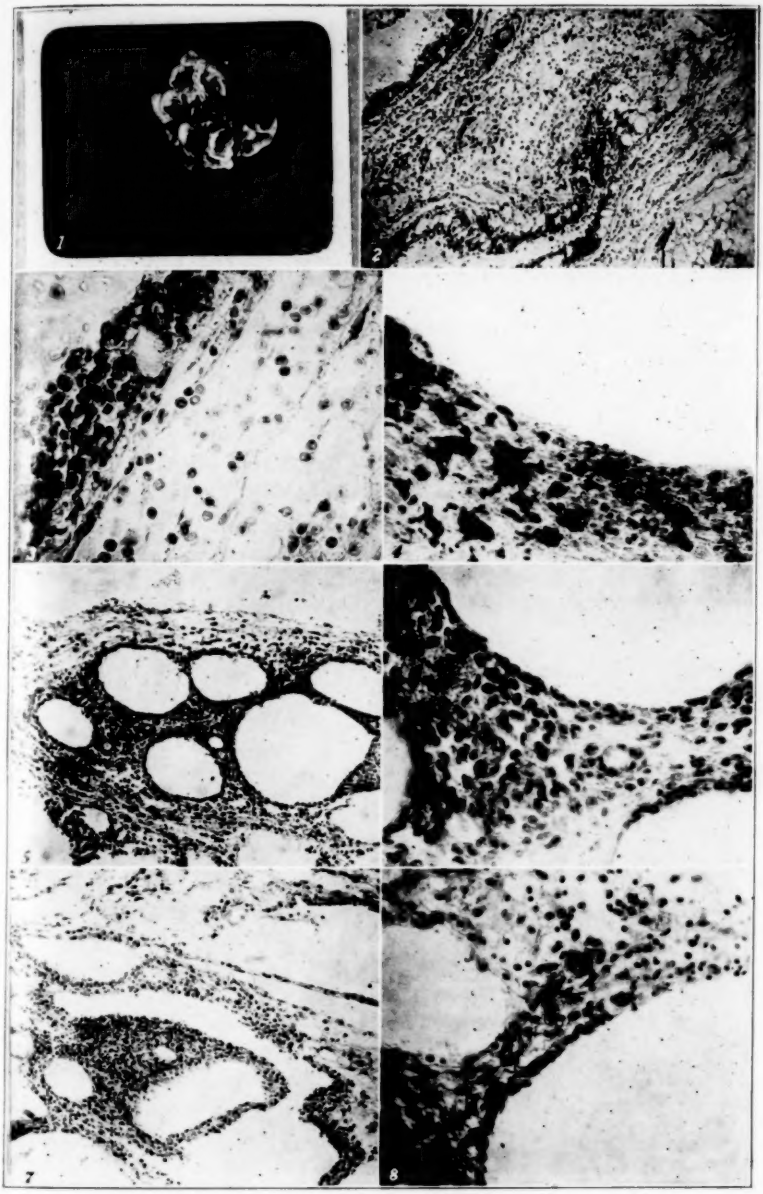

Fig. 1.—Carefully dissected 9 day old oil tumor from subcutaneous tissue of rat.

Fig. 2.—Low power photomicrograph of section of oil tumor 24 hours old.

Fig. 3.—High power photomicrograph of section of oil tumor shown in Figure 2.

Fig. 4.—Photomicrograph of section of 24 hour old oil tumor that has been fixed in formaldehyd, cut with the freezing microtome, stained with sudan III and hematoxylin and cleared in glycerin. The oil has fallen out of the cavity. The small droplets are seen between the cells in the wall.

Fig. 5.—Low power photomicrograph of section of 48 hour old oil tumor of rat.

Fig. 6.—High power photomicrograph of section of oil tumor shown in Figure 5.

Fig. 7.—Low power photomicrograph of section of 7 day old oil tumor of rat.

Fig. 8.—High power photomicrograph of section of oil tumor shown in Figure 7.

eosin. At this early stage, one saw the oil carefully cut off from the surrounding fibrils of the fibrous tissue by a layer of cells varying from 1 to several cells in thickness. The whole of the surrounding tissue was filled with cells evidently migrating toward the oil. The immediately adjacent cellular capsule was ragged; the cells were not closely matted together in it. A few had penetrated a short distance into the oil (Fig. 2).

In studying more carefully the various parts of these sections, it was interesting to note that the extent of this cellular reaction varied in the different tissues into which the oil had been placed. It was much greater about the drops placed in the more cellular fibrous tissue than in the fat tissue.

The types of cells responding in most areas were chiefly large spherical or ovoid cells having a well formed vesicular nucleus. Among these larger round cells in most areas one found also a scattering of small mononuclear cells, a few polymorphonuclear neutrophils and a larger number of polymorphonuclear eosinophil cells (Fig. 3). The relative number of the latter cells also varied with the regions into which the drops were placed. Among the more numerous blood vessels of the subcutaneous tissue, one saw a larger proportional number of lymphocytes and leukocytes than in the less vascular fibrous tissue and fat.

With this movement of cells toward these drops of fat, tiny droplets of fat were continuously breaking off from the larger one and moving out into the tissue. This moving out of small fat drops was in proportion to the movement of the cells toward the larger drops. These small fat droplets could be readily brought into the field of vision at all periods of the development of these tumors by staining the frozen formaldehyd fixed sections with sudan III and hematoxylin and clearing the section with glycerin (Fig. 4).

At first we thought that these large mononuclear cells with a vesicular nucleus were wandering cells of some sort or another, as many other authors have considered them. It soon became evident, however, that this was not true. As seen in the section of the tumor taken at a later period, these cells were fibroblasts that had loosened from their attachment to their intercellular fibrils and endothelial cells, which had separated themselves from the capillaries through the action of the oil on them.

By means of the tissue culture, it was possible to determine fully that the shape of the fibroblasts is not determined by any internal organization peculiar to them, but to chemical and physical reactions that they induce in the environment about themselves. They are simple fluid systems. When connective tissue cells are placed in body fluids containing fibrinogen, they coagulate the fibrinogen to fibrin and stick to the side of the fibrin fibrils. They are fastened to the fibrin by the ergusia. These fibrin fibrils, as Hertzler [25] has shown, become the intercellular fibrils of the connective tissue. The oil dissolving this ergusia not only loosens these cells from their attachment to the fibrils, causing them to round off as any drop of fluid rounds off under these conditions, but it also draws them to it. At later periods after the oil droplets have become saturated with the ergusia, the cells slowly assume other shapes according to the shape of the proteins which they coagulate in their environment.[23]

EXPERIMENT 2.—Four rats were injected the same as in Experiment 1, and the tissue removed was studied and treated in the same manner. The difference between this experiment and the first one was that the tumors were removed after forty-eight hours. At this period the cells had ceased to migrate to any extent from the tissue outside. The cells at the edge of the oil droplets

had become more closely packed together into a layer, several cells in thickness (Fig. 5). The inner layer of cells had in many places formed a continuous layer of cuboidal or flattened cells much like endothelial cells. Outside this inner cuboidal layer, the large mononuclears were stretching out more or less in many places to spindle and irregular shaped cells. These changes were suffered only by the large round cells with vesicular nuclei. The lymphocytes and leukocytes remained scattered among them as before (Fig. 6).

EXPERIMENT 3.—In this experiment one rat was injected in the same manner as the others. The tumor was removed after three and one-half days. It showed no important differences in its morphology from those removed after forty-eight hours.

EXPERIMENT 4.—Four rats were injected as in the other experiments. The tumors were removed after seven days. At this period the picture had changed little from that of the earlier periods, except for a further organization of the cells about the fragment into a definite connective tissue (Fig. 7). Most of the large mononuclear cells were stretching out to take a spindle shape along the forming intercellular fibrils, or had alined themselves into a layer of flattened or cuboidal cells about the oil droplets (Fig. 8). The fine intercellular fibrils noted in the specimen removed at forty-eight hours (Fig. 6) had now become more prominent; a true intercellular fibrous tissue had made its appearance in many places (Fig. 9). Most of the polymorphonuclear and small lymphocytes still remained scattered among these cells. They had taken no part apparently in the actual formation of the capsule, however.

EXPERIMENT 5.—Twenty-two rats were injected as in the other experiments. The tumors were removed from these rats under ether at fourteen days, one month, two, three and seven months. The tumors were fixed either in formaldehyd or Zenker's fluid and stained with hematoxylin and eosin or hematoxylin and sudan III. In most of the specimens the changes were a gradual increase in the organization and then a hyalinization of the capsule about the oil droplets. The oil remained unchanged during this later period (Figs. 10, 11 and 12).

While the oil remained unchanged in practically all these cases, in one rat it was apparently absorbed. This absorption took place slowly, and as the oil disappeared the circumference of the cellular wall either shortened or the tumor collapsed. It was interesting to notice that the cells in the capsule of such cases of absorption did not tend to lay down intercellular substances but remained closely packed together much the same as they were at the beginning. They also showed some evidence of growth in that their nuclei contained more chromatin and their cytoplasm stained more deeply (Fig. 13). Mitosis also was observed in one of these cases. There was never any evidence of the oil stimulating the cells to grow in any of the other cases. The oil attracted the surrounding cells of the tissue to it, but it did not excite growth in these cells. It acted rather to cause them to degenerate. Evidences of growth were seen in these sections only when the oil was placed in a sufficiently cellular tissue so that a large number of cells became massed at its periphery. When the number of cells became large enough, as in Figure 15, then one saw sharply staining cells. Growth in these cases is evidently a secondary phenomenon and the result of the massing of the cells together. It was secondary to the original action of the oil which pulled them into this mass.

EXPERIMENT 6.—One dog was injected in the same manner as the rats. The tumor was removed after three weeks. It was interesting that in this animal the oil was being slowly adsorbed as in the case of the one rat described above (Fig. 14). The cells about the absorbed oil droplet showed evidences of stimulation. The conditions leading to growth and the absorption of the oil in these cases were not determined.

EXPERIMENT 7.—One monkey was injected with 5 c.c. of Mazola oil. The tumor was fixed in formaldehyd after nine days. The oil had broken up into numerous droplets. Each of these tumors was enclosed in a cellular fibrous

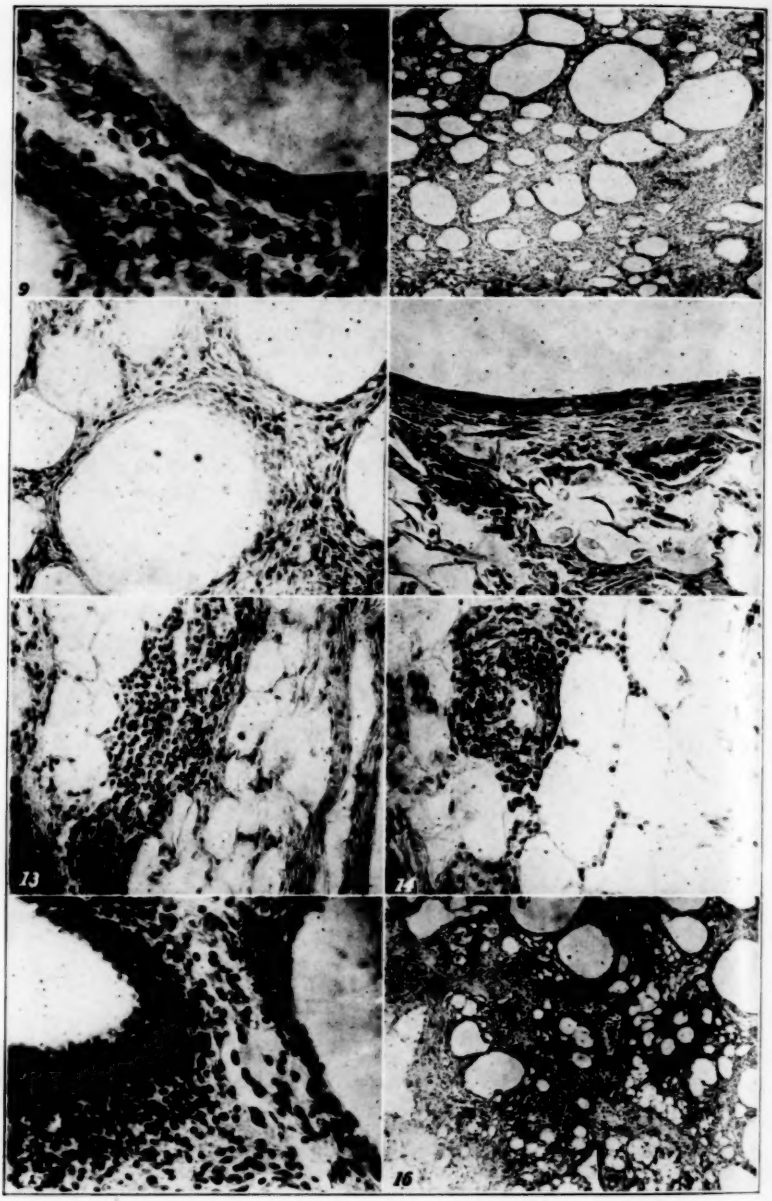


Fig. 9.—High power photomicrograph of another part of section of oil tumor shown in Figures 7 and 8.

Fig. 10.—Low power photomicrograph of section of 22 day old oil tumor of rat.

Fig. 11.—Low power photomicrograph of section of 7 months old oil tumor of rat.

Fig. 12.—High power photomicrograph of section of 24 day old oil tumor of rat.

Fig. 13.—Mass of cells marking site of oil cyst in which the oil was absorbed.

Fig. 14.—Section of wall of oil tumor from subcutaneous tissue of dog; the oil has been absorbed and the circumference of the tumor has reduced accordingly.

Fig. 15.—Dense mass of cells at edge of oil droplet showing evidence of growth in 7 day old oil tumor of rat.

Fig. 16.—Low power photomicrograph of section of 9 day old oil tumor from subcutaneous tissue of monkey.

capsule like that seen in the majority of the rats. None of the oil had been absorbed (Fig. 16).

EXPERIMENT 8.—Two rats were injected with pure Mazola oil that had not been sterilized. The tumors were removed after seven days. The picture in these cases was different. The oil was surrounded by a mass of fibrinous exudate filled with polymorphonuclear cells. This typical inflammatory reaction was quite different from the picture of the simpler migration of wandering and fixed tissue cells to the sides of the sterile oil droplets.

Mook and Wander noted giant cells in the hyaline capsule surrounding droplets of paraffin oil. They considered that the oil acted as a foreign body. They called these giant cells foreign body giant cells. The tumors they classified as sarcoids.

It must be pointed out that paraffin oil applied frequently to a given place in the skin will lead to cancerous production. What Mook and Wander studied were single injections. The oil that had been injected in many of their cases was not pure paraffin oil, but oil containing camphor. This substance excited a true inflammation. There was an exudation of fluid and fibrinogen from the blood vessels, and when necrosis intervened polymorphonuclear cells made their appearance.[54] The fibrinogen and fluid formed a thick mass about the irritant or diluted it. The fibrinogen clotted to a gel. As stated above, oxygen diffused readily into such clots no more than from 0.5 to 0.7 mm. The cells become abnormal beyond this distance from the source of oxygen. Barta[55] has recently studied these abnormalities and finds that cells situated a distance greater than 0.7 mm. from the air surface of the layer of plasma medium of a culture change into reticular, epithelioid and giant cells. These cells are not in any way concerned with foreign bodies but owe their formation entirely to a reduction in their oxygen supply. Fibroblasts, certain wandering cells and other tissue cells will show these changes. The giant cells noted by Mook and Wander can only be indicative of such an inflammatory process. This same inflammatory process we noted about drops of unsterile corn oil. The sterilized oil acts only to dissolve the ergusia of the cells. Since the ergusia has strong affinities for the oil as well as the cells, the oil is thus drawn toward the cells and the cells to the oil. The larger oil droplets become encapsulated by drawing the cells to them from the tissue and blood vessels in proportion to the original number of these cells in these localities. Smaller droplets of fat are seen among the cells. They are drawn from the larger drops by the same process that the cells are drawn to these larger drops.

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54. Burrows, M. T.: Neuritis of the Cranial Nerves in Lethargic Encephalitis and the Differential Anatomic Diagnosis Between It and Acute Poliomyelitis, Arch. Int. Med. **36**:477 (Oct.) 1920.

55. Barta, E.: Experimental Histological Studies, II, Giant Cell Formation and Fat Metabolism in Relation to Oxidation (Lymph Nodes in Vitro), to be published.

While many previous authors have looked to the discovery of some hormone or growth stimulating substance in coal tar and other lipoids capable by long use of inducing cancer, others have appreciated that such is probably not the case. They had noted that the oil acts to cause the cell to degenerate rather than grow (Bullock and Rohdenberg [9] and Champy [10]). What stimulated the eventual proliferation of these cells they could not determine. The tissue culture has answered this question. It is the result of the crowding of cells induced by the oil attracting the cells of the tissue to it away from their intercellular substances and blood vessels.

It is now well established that to induce cancer with coal tar and other lipoid solvents these substances must be applied frequently over a long period of time. The reason for this is clearly shown above. A single drop of oil becomes quickly saturated with the ergusia, or lipoid substance, of the cell. It can pull only a few cells to it. With each addition of fresh oil to the same place, more cells are pulled in until finally there is built a stagnant mass of cells of sufficient size to overcome the growth energy of the surrounding tissue.

## COMMENT

Previous work on cancer has shown that it may be induced by a variety of conditions and substances: It follows on the site of chronic inflammation; it may arise in many benign congenital and other types of benign tumors and congenital defects; it may be induced by coal tar, other lipoid solvents, roentgen rays, radium, bacteria and certain animal parasites. While many of these substances and conditions were shown capable of inducing cancer, it was also noticed that they are unimportant in the eventual course of this disease. Cancer is an independent growth of body cells which may be induced by any one of these conditions and substances but, once established, then proceeds independently of them. The first important problem to be solved in cancer is the conditions allowing such an independent growth of the cells.

This problem was investigated by one of us (M. T. B.) by means of the tissue culture. It was found that single cells cannot grow in a simple body medium, such as blood plasma. Growth can intervene in this medium only about densely cellular fragments and it proceeds about these fragments only when they are placed in a very small stagnant quantity of this medium, which is well supplied with oxygen. This growth depends on the accumulation and maintenance of a certain concentration of a primary product of the cells about them. This product is formed by them through the oxidation of food materials. It is soluble in the blood, in serum and in isotonic sodium chlorid

solution. This substance or substances has been called the archusia, or the laboring substance, of the cell.

The body cell is a drop of fluid cytoplasm in which floats a fluid nucleus. It also contains fat droplets, centrosomes, mitochondria and other formed bodies floating in its cytoplasm. These cells have no organization other than centrosomes (active only in cell division) for transforming their energy into work. These cells can induce reactions between certain food substances and oxygen with the formation of the archusia. The archusia acts on the cell in proportion to its concentration. In low concentrations ($S_1$) it has no effect. In a medium concentration ($S_2$) it acts to liberate another substance from the cell's protoplasm, the ergusia. The ergusia is a lipoid soluble substance readily adsorbed by fats and proteins. Small mobile particles of proteins and fats are drawn into the cell as this substance is liberated into a medium in which it can diffuse. Larger masses of proteins and fats draw the cells to them. The cell grows by this ability to take up these proteins and fats. Its migration is the result of the same reaction and occurs when the cell meets masses of proteins and fats having a greater inertia than itself. The ergusia is not the same in the different cells. It is highly selective in its action on proteins but not on fats. All cells are attracted by fats. The ergusia of the connective tissue cells coagulate fibrinogen to fibrin while the ergusia of the leukocytes and lymphocytes does not. The different cells in the body differ from each other in their chemical make-up. They grow always to reproduce themselves. This specificity in their growth may be readily referred to the specificity of their ergusia and the specific selection of food substances by it.

In high concentrations the archusia ($S_3$) causes the proteins and fats to be digested; the cell grows and divides by mitosis. In all higher concentrations ($S_4$) the cell is digested and destroyed.

The archusia is apparently the same in all cells. The archusia extracted from one cell sets up the reactions mentioned above in other cells. None of these cells except possibly the striated adult muscle fibers can retain their archusia. For them to grow independently they must be crowded, therefore, into a small stagnant area in which their archusia cannot escape from about them. Since the archusia is not specific, these same cells can be made to grow dependently, however, by supplying archusia from the outside. In such cases their growth must be limited always to the supply, and wholly under the control of the outside forces supplying this substance.

In the light of these facts, it became evident that cancer may be none other than the result of a primary reorganization of tissue in the body. There was no evidence that the independently growing cells of the culture had changed primarily. The change leading to their growth

was in the environment. Applying these principles to the study of growth as it is observed in the body, it became evident that all growing tissues of the normal organism are cellular and have a stagnant circulation and that this stagnation and cell crowding reaches its greatest development in cancer. The question therefore arose, Is cancer other than the result of the building of a dense mass of cells free from blood vessels? The proof of this deduction lay in showing that such a mass once built will reproduce itself and that the substances and conditions that lead to cancer act only to build such a tissue organization.

It was found by means of the culture and a study of wounds that any dense, stagnant mass of tissue may not only grow but also destroy readily any less dense and stagnant tissue. Not only the surrounding tissue cells but also blood vessels suffer in this destruction. Such a mass once established can thus continuously reproduce itself through a growth of its cells and the continuous destruction of its blood supply.

The action of coal tar and corn oil in the production of cancer have been investigated. It has been found that they have no stimulating action on the growth of the cells, but act only to disrupt the normal organization of the tissue and build a densely cellular tissue relatively or wholly free from blood vessels and intercellular substances. These oils act to collect these cells merely by dissolving the ergusia, the lipoid-like substance of the cell. The cells are drawn to the edge of the drop merely through this adsorption by the oil of their ergusia. The ergusia liberates the energy for the migration of the cell, through its strong affinities not only for the cells but also for the oil. It thus decreases the surface tension of the cell in the presence of the oil.

A single drop of coal tar, corn oil or paraffin is limited in this capacity. It soon becomes saturated with the ergusia. It cannot draw a sufficient number of cells or form a sufficiently large mass of these cells for them to overcome the resistance of the outside and thus take food to themselves. With each new addition of the oil, more and more cells are drawn to the drop until a cancer is built.

We have not studied the action of roentgen rays, radium and animal parasites in the laboratory. It must be pointed out here, however, that the only tapeworm larva known to induce cancer is the cysticercus of the cat tapeworm. This larva produces changes in the tissues of the host which are different from those produced by the larvae of tapeworms, which do not induce cancer. It induces a densely cellular tissue capsule about it. This capsule is a dense mass of fibroblasts, while that induced by the echinococcus, a noncancerous producing parasite, is a hyaline, fibrous one containing very few cells. Wolbach,[56] in 1909, had shown that the roentgen ray acts on the tissue to reduce

56. Wolbach, S. B.: The Pathological Histology of Chronic X-Ray Dermatitis and Early X-Ray Carcinoma, J. M. Res. **21**:415, 1909.

the blood vessels and change them. It acts, therefore, also to build a cancerous organization.

Bacteria are now being studied carefully. They act differently from the tar to produce, however, the same nonvascular cellular organization in the tissues. Smith had noticed that *Bacillus tumefaciens* when introduced into the tissues of a plant induces the cells to proliferate actively. In studying the action of this organism in the animal, we find it causes the cells with which it comes into contact to proliferate without the formation of normal body structures, such as the blood vessels and intercellular substances. It acts to produce by proliferation a local dense mass of cells that is identical to the masses formed by the drops of oils through collecting the scattered cells of the tissues about them. Extracts of embryo and Berkefeld filtrates of malignant tumors, which are rich in archusia, act in the same manner to stimulate the tissue cells to proliferate. Drops of oil act to disrupt the normal organization of the tissue and build one peculiar for cancer in that they are able to attract the cells from the tissue to them (Fig. 17). The bacteria produce the same organization by stimulating the cells that lie between the blood vessels to proliferate and thus to form a crowded cellular mass (Figs. 18 and 19). The blood vessels do not grow to any extent because the stimulus is continuously washed away by them and cannot concentrate on their lining endothelial cells.

The latter experiments on the action of bacteria are interesting in that they show that certain bacteria can liberate growth stimulating substances not unlike those liberated by body cells.

In the further study of the properties of tissue cells, it has been shown that these simple active fluid systems when polarized or placed in an environment in which the archusia can concentrate only at one of their ends, suffer a rhythmic explosive breakdown of either the ergusia liberated at the one end where the archusia is high or the substance adsorbing it in the environment. These breakdowns are expressed in muscle by contraction, in the gland cells by secretion, in the nerves by conduction. Function is the result of such a polarization. In the body this polarization is induced by the interspersion of blood vessels between double columns of cells. In the culture function is produced by placing the same conditions about the cells. The blood vessels bathing one end of the cell remove the archusia formed at this end of the cell. It accumulates at the other end of the cell away from the blood stream.

In the light of the foregoing observations, cancer maintains when the cells are crowded together in an area having a greatly reduced blood supply. Function is a property of a rich blood supply in properly arranged blood vessels. It is something which takes place at the expense of the growth reaction of the cells. It reaches its greatest development in an environment that must inhibit growth completely

unless the cells are supplied with archusia by other means. Function is something which has been imposed on the cell by outside forces and not something which the cells will tend to develop at their own initiative. The question confronted us, What is the nature of these outside forces?

As has been noted, single cells isolated in a drop of plasma and groups of cells washed with a stream of serum cannot grow. The same

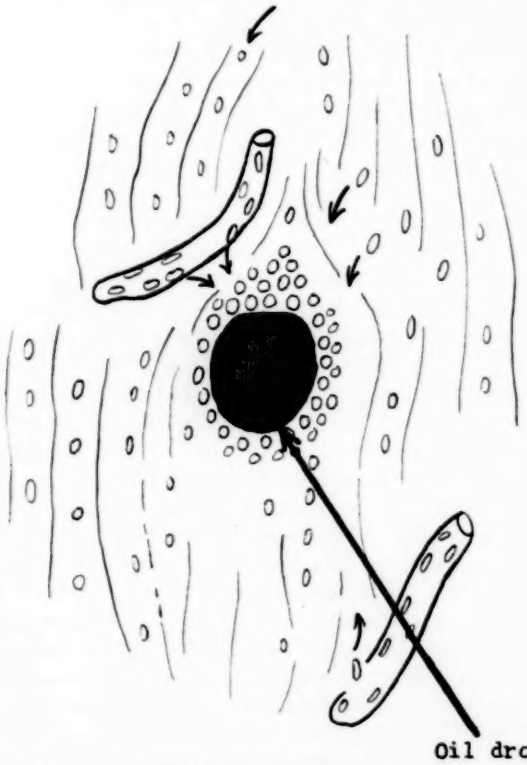


Fig. 17.—Manner in which a drop of oil attracts cells when placed in the tissue; it disrupts the normal organization of the tissue and builds a cancerous organization.

cells can be made to grow by adding archusia to these mediums. As stated above, such growth is not independent but dependent on the source of the archusia. In the animal organism there is no evidence to show that the cells lose their power to grow at any time. The prevention of an active, independent growth of these cells and function in the normal organism is wholly dependent on the organization of the normal organism, the arrangement of its blood vessels and cells.

In other studies in this laboratory, it has been found that the cells of the normal body do not grow independently at any time from the egg to the death of the adult. At no place are they crowded sufficiently and their environment sufficiently stagnant to allow them to grow without an outside source of archusia. In cancer conditions are different; the organization about the cells has changed to one in which the cells are crowded sufficiently and their relative circulation sufficiently reduced for them to form enough archusia and retain it in a concentration ample for them to grow independent of any outside source.

In the light of these facts it becomes evident, therefore, that growth in the body must be at all times dependent on a source of stimulus from

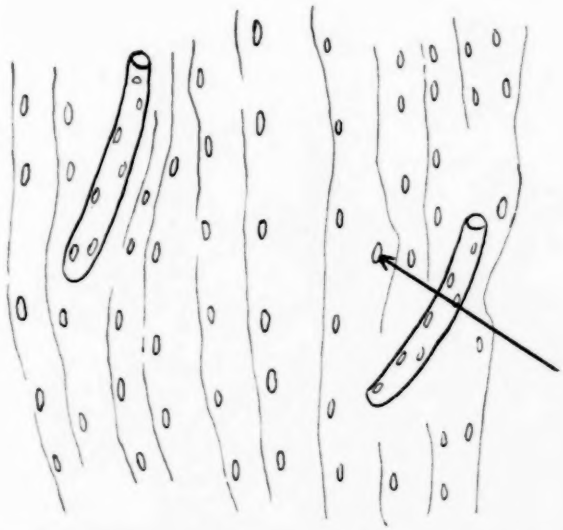

Fig. 18.—Site of introduction of tumor forming micro-organism or extract of an actively growing tissue.

the outside: the mother, the yolk of the egg or the food. It is a well known fact that one cannot exist on proteins, fats and carbohydrates alone. Other accessory food substances are necessary. These have been termed vitamins. It has been shown above that when *B. tumefaciens* is introduced into the tissues it stimulates the cells to proliferate. They grow to form a densely cellular nonvascular mass. The same is true for extracts of embryos or any other actively growing tissue. Under normal conditions these substances cannot gain entrance to the body except through the food. In the food they must enter the blood vessels first and then gain access to the cells. Under such conditions they will not act to build a cancerous organization. The blood vessels must

suffer the greatest stimulation. They must grow, therefore, in excess of the cell between them and form a vascular rather than a nonvascular tissue.

In the light of these facts, it became of interest for us to study the action of *B. tumefaciens* and the extracts of embryos when injected and when fed to the animal. One of us had already noted that extracts of actively growing embroyos when injected into the skin stimulate an

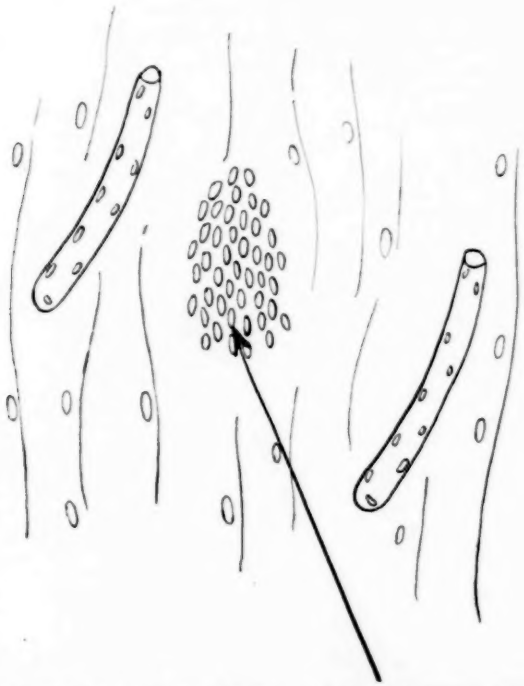

Fig. 19.—Result of introduction of tumor forming micro-organism or extract of an actively growing tissue into the tissues. The cell proliferates without the formation of intercellular substances and blood vessels. These bacteria or tissue extracts by stimulating the cells to proliferate accomplish the same result as oil in attracting the scattered cells of the tissue.

active growth of cells and cancers.[48] We are now investigating the effect on the growth of young rats of feeding *B. tumefaciens* and extracts of embryos.[57]. Two day old and 5 day old cultures of *B. tumefaciens* (Smith) were fed to rats in a diet free from vitamin B and in a diet free from vitamin A. The rats fed on 2 day old cultures in a

57. Burrows, M. T.: Studies to Determine the Biological Significance of the Vitamins, Proc. Soc. Exper. Biol. & Med. **22**:241, 1925.

diet containing vitamin A (butter) grew as well as those fed on the same diet containing autolyzed yeast instead of the bacillus. The rats fed on the 5 day old culture grew as actively. Extracts of embryos that had been shown to be rich in the archusia have also been fed. These extracts act only as vitamin B substitute. In other experiments we have sought for stimulating substances in the glands of internal secretion. The studies on the ovary have now been completed. The Allen-Doisy hormone extracted from the follicular fluid of the ovary is found to be rich in an active growth stimulus. Whether this stimulus acts as substitute for the vitamins we have not determined.

From these observations on the effect of feeding these substances on the growth of the animal, it becomes evident, therefore, that the control of body growth, its form and function must depend on three factors: (1) a complex egg cell capable of giving rise by division to multiple cell types; (2) an absence of the power of the cells of the body to retain their archusia, and (3) an active supply of archusia from an external source aided probably by certain glands of internal secretion.

It has been possible for us to show in the laboratory that when a stimulus is introduced into the tissue it stimulates an active growth of cells and a cancerous organization. When fed it produces a normal vascular tissue. When placed in the tissue it stimulates the cells to grow without organization. From the food it enters the blood vessels first, and stimulates them to grow more than the intervening tissue cells. A vascular-functioning tissue is thus formed.

The bodies of higher animals must be, therefore, the result of an evolutionary development. Their function and normal growth is not a property peculiar to their cells, except in an environment rich in growth stimulating substance, the archusia or something similar. This substance forcing its way in from the outside builds the vascular system. Function is not a normal act of the cells, but something imposed on them by the body organization thus controlled from without. The bodies of higher animals survive, grow and function only through this outside aid. Such stimulants are formed probably only by living cells. The body exists through preying chiefly on lower nonfunctioning growing forms. While the glands of internal secretion must aid in the directing of these stimuli, the chief source of these stimuli is probably from without.

In the cancerous state the cell alone reaches its full independence. In further proof for this deduction, it is interesting to note that Cramer [58] has found that the growth of transplanted tumors of rats is not influenced by the absence or presence of vitamins. We have

58. Cramer, W.: Dietary Deficiencies and the Growth of Cancer, Eighth Scientific Rep. Imper. Cancer Res. Fund, London, p. 17.

repeated and confirmed these experiments.[59] In cancer the cells are able to live an existence independent of specific substances in the diet. In the crowded, stagnant environment of cancer they can conserve their energy, the archusia, and build their parts from simpler substances.

The cancer cell is not primarily different from the normal cell. The primary change in cancer is a reorganization of the tissue so as to produce a densely cellular mass having a relatively poor circulation. While it has been shown from the work of Nuzum,[16] Blumenthal, Auler and Meyer [15] that a certain number of cancers of man undoubtedly owe their origin to bacteria, it must be clearly emphasized here that this does not indicate that cancer is infectious. Cancer may be produced by any one of a number of conditions and substances that primarily build a dense mass of cells in the organism in such a manner that the circulation is so reduced that this mass receives at its periphery an ample oxygen supply, but is otherwise stagnant. The conclusions drawn by Oxner [60] and Nuzum [16] are not based on the facts at hand and are thus wholly uncalled for and may do harm.[61] Blumenthal, Auler and Meyer have carried their work further than Nuzum. They found it impossible to draw such conclusions.[62] Cancer is the normal means of the cell to survive when unaided from without. It must always be the normal outcome of a certain number of aging organisms.

The difference between the cancerous tissue and the normal is the difference between the greater conservation of growth energy in the cancer than in the body outside. Our immediate hope for the medical treatment of cancer does not lie in an ability to equalize the energy in the body over that in the cancer, but in finding some means to overwhelm the growing cancer cells. If we raise the amount of archusia in the blood to that in the cancer, the growth of the cancer must cease, but function cannot maintain under these conditions. Function depends on the absence of, or a very low, archusia at the end of the cell in contact with the blood stream and a high value at the opposite end. The amount of function is the difference in these energy values. When we demand increased function, the circulation increases. When we eat a big dinner and load our blood with growth stimulus from without, we become

59. Burrows, M. T., and Jorstad, L. H.: Unpublished notes.

60. Oxner, A. J.: Cancer Infection, Surg., Gynec. & Obst. **40**:336, 1925.

61. Soper, S. A.: The Application of Facts and Opinions Resulting from Laboratory Experiments to the Practical Work of Cancer Control, Surg., Gynec. & Obst. **40**:334, 1925.

62. The same evidently applies to the recent work of Gye and Barnard reported in the lay press and in J. A. M. A. **85**:368 (Aug. 1) 1925, at the time this proof was being corrected. The Rous chicken sarcoma has long been suspected as being due to a bacterium. This is not true of many of the sarcomas and carcinomas of rats and other animals. Gye and Barnard will undoubtedly find that extracts of any actively growing tissue, many bacteria and other substances capable of stimulating cells will induce cancer if properly introduced (Footnote 48).

dull and drowsy. After a day of active blood circulation, we become exhausted, our blood pressure drops, we sleep. The cells must be allowed to grow, to recuperate their loss of substance through function.

We have found, however, that when the archusia is raised in the medium of a tissue culture to a certain high concentration ($S_4$) the cells are digested. Cancer cells and actively growing embryonic cells can be made to suffer such digestion by adding to the medium containing them only one-tenth of the amount of archusia capable of stimulating growth in fresh normal adult tissues. Whether this can be used for treatment is yet to be investigated. It is possible that other more simple means will be found to destroy the cancer without destroying normal cell. The means to discover such substances or condition will probably be found in a more careful analysis of roentgen rays and other substances inducing cancer and in more study of the details of cellular growth and function.

## CONCLUSIONS

1. The tissue culture has given us an entirely new idea of the structure and activity of body cells. Our earlier ideas had been gleaned entirely from a study of complexly organized unicellular organisms and a study of the morphology of body cells. The tissue culture has allowed us to study for the first time the mechanism of growth and function in these cellular elements. They are one of the few cells in nature which have a simplicity of structure sufficient to make such an analysis.

2. Cancer is an independent growth of these cells. It may be induced by any one of a number of conditions and substances. Once established, it proceeds independently of these causative agents.

3. An active independent growth of body cells depends on a crowding of the cells together in a stagnant area or an area having a relatively poor blood supply. Cancer has this kind of an organization.

4. It has been found that such an organization can reproduce itself through the fact that it destroys through its growth the normal tissue and blood vessels about it.

5. The action of drops of corn oil and coal tar on the tissue has been investigated. It has been found that they act to build a dense, stagnant mass of cells by drawing the tissue cells to them and away from their intercellular substances and blood vessels.

6. The bacteria that induce cancer act in the same manner to build a densely cellular stagnant mass of cells, but by a different means. They induce such a mass of cells to form by stimulating the cells of the tissue to proliferate without forming to any extent intercellular substances and blood vessels.

7. These factors of stagnation and cell crowding become important for growth because the growth of body cells depends on a certain con-

centration of a primary product of the oxidation of the cells, the archusia. This substance is soluble in blood. The cells cannot retain it in quantity. Its concentration is at all times under the control of the environment.

8. Function is likewise determined by the environment. It maintains in an environment rich in blood vessels so placed that they pass close to one end of the cell. The other end of the cell away from these vessels accumulates archusia and is active. The end near the vessels is inactive. Function is the result of an explosive breakdown of such a polarized cell. This was proved by a direct analysis of isolated functioning cells in the cultures.

9. Body cells can be made to grow not only through the accumulation of their own archusia, but by adding archusia from outside sources.

10. Function is something that maintains only in an environment that inhibits an independent growth. It occurs only in a richly vascularized tissue. Function is something imposed on the cells of the body. For them to survive in such a state they must be supplied with growth energy from other sources. This functioning tissue is formed and maintained by growth stimuli entering the blood vessels from the digestive tract. These stimuli act in the capacity of vitamins. They represent the growth energy of other living things.

11. Cancer maintains without these accessory food factors.

12. The functioning organism is evidently the result of an environment rich in growth stimulating substances supplied by preexisting lower growing and nonfunctioning forms.

13. In cancer the cell becomes independent. The cells in the aging organism must tend to revert to this state. Any tissue may be made cancerous by anything that frees the cells of the effect of their intercellular substances and an active circulation of blood.

# THE VALUE OF IRON IN ANEMIA

## AN EXPERIMENTAL STUDY *

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AND
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The question of the absorption and utilization of iron in the formation of hemoglobin has long engrossed the attention of clinicians and physiologists. Unfortunately the results of these researches are far from being in accord in spite of the great amount of labor expended.

If we leave out the earlier work as for the most part too inaccurate to be of service, the modern study begins with Bunge,[1] under whose direction Haeusermann studied the question exhaustively. His plan was to feed growing animals food low in iron, generally rice and milk, half of the animals receiving in addition medicinal iron (ferric chlorid). After several months' treatment, the animals were killed and the total hemoglobin determined, and in some of the animals the total iron also. He found that the animals became highly anemic on rice and milk, and that those receiving iron in addition contained no more hemoglobin than the controls. Furthermore, the animals receiving iron had no more total iron in their bodies, except in one experiment. His results on rabbits and dogs were discordant, for after one or two months' feeding he could not determine whether iron was not stored up through lack of absorption or absorbed and then eliminated.

Abderhalden,[2] in an extensive series of researches, came to the conclusion that animals on an iron-poor diet plus medicinal iron failed to produce as much hemoglobin as animals on a diet rich in food iron. On the other hand his observations led him to the view that medicinal iron in some way stimulated, for short periods of time at least, the formation of hemoglobin from the food iron. Tartakowsky,[3] however, came to the conclusion that medicinal inorganic iron is both absorbed and utilized in hemoglobin formation. It is worthy of note that his young animals fed on rice and milk became anemic and finally ceased to grow, but that medicinal iron added to their diet caused the blood to gain in hemoglobin and the animals to grow again. He considers that Abderhalden's results should likewise be interpreted in this sense. Schmidt [4] came to substantially the same conclusions as Tartakowsky.

* From the Department of Medicine of the University of Illinois College of Medicine.

1. Bunge: Physiological Chemistry, Chapter 25.
2. Abderhalden: Physiological Chemistry, Ed. 3, Chapter 35.
3. Tartakowsky: Arch. f. d. ges. Physiol. **100**:586, 1903; ibid. **101**:423, 1904.
4. Schmidt: Verhandl. d. Deutsch. path. Gesellsch. **15**:91, 1912.

In criticism of this work, it seems quite clear that many of the animals were on an inadequate diet, not only in respect to vitamins but also in some cases in respect to proteins and fat as well. Many of their results were certainly due to deficiency diseases rather than to the lack of iron only.

Recently there has been a revival of interest in the subject. Whipple [5] and his associates have studied the question anew and along somewhat different lines. They have shown that the diet of the animals was of the very greatest importance, and their experiments have given no support to the value of inorganic iron in simple anemias. Musser [6] also has reported some experiments which failed to show any favorable influence of inorganic iron in experimental hemorrhagic anemias. On the other hand, Scott and Barcroft [7] state that iron seems to "anticipate the cure, which occurs normally." Gibson and Howard,[8] while admitting the superiority of a diet rich in food iron, say, "We still feel justified in continuing the administration of iron in the form of Blaud's pills." From this it may be inferred that these authors consider inorganic iron as of value, or at any rate that the contrary has not been satisfactorily demonstrated.

It seemed to us that, in view of the discordant results obtained by different authors, the subject should be reinvestigated, with the emphasis laid on the following points: (1) to select an animal that can be obtained in large numbers in large litters, the individuals of which are practically identical; (2) to use these animals in sufficient numbers to eliminate the varying results, which must necessarily obtain when only a dozen or two are used; (3) to use a standard basal diet adequate in all respects; (4) to continue the experiments over a time sufficiently long to ensure decisive results, and (5) in determining the hemoglobin, to use a method of the highest possible degree of accuracy and free from the defects of the usual colorimetric methods.

To comply with the first point, we selected the rat, because its life history is thoroughly known, and we secured all our animals, with the mothers, when only a few days old. All were of the same breeding. To cover the second point, we used several hundred animals, 386 rats and thirty-two dogs. The diet used was the standard casein diet of Osborne and Mendel, yeast being added to carry vitamin B, and on this our rats

5. Whipple, G. H.; Robscheit, F. S., and Hooper, C. W.: Blood Regeneration Following Simple Anemia, Am. J. Physiol. **53**:151-263 (Sept.) 1920.

6. Musser, J. H., Jr.: Influence of Inorganic Iron on Regeneration of Blood After Hemorrhagic Anemia, Arch. Int. Med. **28**:638 (Nov.) 1921.

7. Scott and Barcroft: Biochem. J. **18**:1, 1924.

8. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, Arch. Int. Med. **32**:1 (July) 1923.

grew and reproduced normally. The iron-free diet was obtained by simply leaving out the ferrous lactate from the salt mixture used in making up the foregoing diet. As thus constituted, analysis showed the iron content to be 0.072 mg. per hundred grams of food. While for convenience we speak of this as the iron-free diet to distinguish it from the iron-containing diet, to which ferrous lactate has been added, it is in reality only an iron-poor diet. To satisfy the fourth point, most of our experiments were continued over several months and always until satisfactorily uniform results showed that a longer continuance would be productive of no further changes. Some of the experiments were continued as long as eight months. To comply with the fifth point, we chose the spectrophotometric method of determining the hemoglobin values, since according to Buerker's investigations, it is the most accurate for this purpose. A further reason for choosing this method was that one of us (C. S. W.) had previously conducted an extensive research based on this method, and was therefore thoroughly familiar with the technic and various phases of spectrophotometric investigations.

## PRINCIPLES INVOLVED IN QUANTITATIVE SPECTROPHOTOMETRIC DETERMINATION OF HEMOGLOBIN

Without discussing this method in detail, we shall give briefly the salient points, assuming that the basic principles are already known. The method is based on the fundamental law that for each colored substance the ratio, concentration to extinction coefficient, is a constant. This law is generally expressed $C/E = A$. In our case the concentration $C$ is, of course, the number of grams of oxyhemoglobin in 1 c.c. of the solution examined. The extinction coefficient is the reciprocal of the thickness of solution required to reduce light of the intensity one to the intensity one-tenth. In the spectrophotometer in question (we used the improved Huefner apparatus), the thickness of the layer of solution remains constant, and $E$ is determined by measuring the intensity of the remaining light. This is effected by rotation of the analyzing with respect to the polarizing Nicol. Now it can be mathematically shown that the extinction coefficient, $E$, is equal to $-2 \log. \cos. O$, where $O$ is the angle of rotation just referred to. In order to obtain $E$, we measure the angle of rotation, $O$, necessary to produce equality in the upper and lower fields. This angle is read off on a vernier and from this the extinction coefficient, $E$, is computed, either from a table of logarithms or more conveniently from a logarithmic curve that Buerker has constructed for this purpose.

Since we are always dealing with a solution of one and the same substance, oxyhemoglobin, the concentrations are directly proportional to

their respective extinction coefficients, so that the latter are used as a convenient method of expressing relative concentration. The figures given in our tables are these extinction coefficients obtained in the manner described. If it is desired to convert these into absolute values of hemoglobin, all that is necessary is to multiply these extinction coefficients by a factor known as the absorption ratio, of course making due allowance for the dilution of the solution.

The construction of the apparatus is such that readings of the vernier are taken in two different sectors of the circle, obtained by rotating the prism first to the right and then to the left. Since any lack of adjustment of the apparatus would immediately be made manifest by the failure of these opposed readings to agree, it is obvious that we have here a guarantee of the proper functioning of the apparatus. A minimum of four readings was taken for each determination, and if an extra degree of accuracy was desired ten readings were taken. Much experience showed that if a number of determinations were made on the same day, no perceptible increase of accuracy was obtained with a larger number of readings because of the increased eye fatigue. We elsewhere have discussed the average and probable error of reading and have shown that it was negligibly small. We had a special dark room at our disposal and the entire apparatus was enclosed in a large, hinged, light proof case, so constructed that no extraneous light could reach the eye.

When we consider the high degree of accuracy in the actual reading of the vernier of the apparatus, it is obvious that the error involved in measuring and diluting the blood is likely to be several times as great as the error in reading. Our pipet was an especially constructed and calibrated piece of heavy thermometer tubing with thick walls, delivering 0.03865 gm., or 0.03646 c.c., of blood. This amount may be readily obtained either by a prick of the vein in a dog's leg or by snipping off a bit of a rat's tail. In actual practice we proceeded as follows: Into long necked, glass stoppered flasks of 50 c.c. capacity were measured 4 c.c. of a 0.1 per cent. sodium carbonate solution, using a Mohr 5 c.c. normal pipet. A pipetful of blood was then blown into this and the solution thoroughly agitated, which gave a perfectly clear, transparent fluid. Our pipet was graduated as a delivery pipet, and by blowing with force each time for ten seconds and withdrawing the tip of the pipet from the fluid while still blowing, a high degree of uniformity was obtained. This is shown from the accuracy determinations below. The blood solution was then transferred to the Troegchen and the readings taken as described. A special feature of the spectrophotometer is that by taking a second reading between the bands any deterioration or alteration of the blood can be instantly determined and the specimen discarded.

ACCURACY DETERMINATION

To test directly the precision obtained in practice, a number of accuracy determinations were made from time to time of which two typical ones are given here. A pipetful of blood was taken from a rat's tail, diluted in the manner described with 4 c.c. of sodium carbonate solution, and the pipet cleaned and dried. A second pipetful of the same blood was then taken and diluted in the same way. These were then examined spectrophotometrically with the results given in Tables 1 and 2.

Since the concentrations are proportional to the extinction coefficients, it will be seen that with only two readings on each side of the vernier a high degree of accuracy is obtained.

TABLE 1.—*Accuracy Determination of Solutions of Same Concentration*

| Solution A | | Solution B | |
|---|---|---|---|
| Left | Right | Left | Right |
| 70.2 | 70.3 | 70.4 | 70.2 |
| 70.4 | 70.1 | 70.3 | 70.9 |
| 140.6 | 140.4 | 140.7 | 141.1 |
| Average of readings..... | 70.25 | Average of readings..... | 70.45 |
| Extinction coefficient..... | 0.943 | Extinction coefficient..... | 0.951 |

TABLE 2.—*Accuracy Determination of Solutions of Different Concentrations*

| Solution A | | Solution B | |
|---|---|---|---|
| Left | Right | Left | Right |
| 73.4 | 73.0 | 75.6 | 75.3 |
| 73.0 | 73.3 | 75.8 | 75.8 |
| 73.3 | 73.3 | 75.7 | 75.6 |
| 73.1 | 73.2 | 75.4 | 75.7 |
| 73.1 | 73.3 | 75.6 | 75.4 |
| 365.9 | 366.1 | 378.1 | 377.8 |
| Average of readings..... | 73.2 | Average of readings..... | 75.59 |
| Extinction coefficient..... | 1.078 | Extinction coefficient..... | 1.208 |

In another test we proceeded as follows: One pipetful of blood ($A$) was blown into 4 c.c. of sodium carbonate, a second ($B$) into 4.5 c.c. of ths same fluid. A simple calculation shows that the concentrations in these two cases are to each other 124.42 : 110.71. The two solutions were then examined; the results are given in Table 2.

Comparing these ratios, we find that $124.42/110.71 = 1.124$ and $1.208/1.078 = 1.120$.

For ease in the interpretation of these and subsequent figures, it is convenient to bear in mind that a difference of 0.01 in the extinction coefficient represents a difference of less than 1 per cent. in the amount of hemoglobin. In other words, the two solutions were so prepared that their concentrations were 1.124 : 1, while the concentrations as actually determined were 1.120 : 1, a difference of only a small fraction of 1 per cent.

It must be remembered that while the vernier readings in degrees of an arc are given to show what is actually read, the concentrations of the solutions are not proportional to these but to the extinction coefficients, i. e., to — 2 log. cos. of these arcs. Since these accuracy determinations were made in the ordinary course of the work, they represent the degree of accuracy actually attained and not that which is merely theoretically possible. These demonstrate very clearly the correctness of Buerker's statement as to the exceedingly great accuracy of the method, especially for the comparative determination of hemoglobin, and, of course, since no color comparisons are made there is no standard to change or deteriorate, which is regularly the case with most colorimeters. In addition it has the very great advantage of recognizing at once any deterioration of the solution, such as may result from a slight admixture of alcohol or ether in the cleaning of a pipet, or from long standing. For a fuller discussion of the method as applied to hemoglobin determination, reference should be made to our previous work.[9]

The method used in the determination of iron in the tissues was that of Ripper-Schwarzer.

To summarize, our method of attacking the problem, keeping in mind the foregoing five points, was:

1. To administer medicinal iron orally to rats, with suitable controls; in other groups to administer iron subcutaneously, and to compare the amount of hemoglobin in the blood and tissues of these with a group of noninjected controls.

2. To repeat these experiments in rats rendered anemic by single or multiple bleedings.

3. To determine the effects on the blood of young rats of medicinal iron administered to the mothers during the periods of gestation and lactation.

4. To control the results of the foregoing by similar experiments on a different type of animal (dog), as well as to study the effects of intravenous injections of iron, for which purpose the rat is ill adapted.

Our division of work was such that one of us (C. S. W.) carried out all the spectrophotometric work; the other (H. N. E.) carried out all the iron determinations and assumed the entire charge of the animals.

### EXPERIMENTS ON RAT GROUP 1 (FORTY-FIVE RATS)

A group of forty-five rats from five litters was divided into two groups, half of each litter placed on our standard iron-free diet, and half on the iron-containing diet already described. They were kept on these

9. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505-528 (Oct.) 1916.

two diets from March 5 to September 24, about six and one-half months. Several hemoglobin determinations were made on dates between these extremes, but to simplify the tables and to save space these are not given. They showed, however, no significant change. It may be stated here, to apply to this group as well as to the other subsequent rat groups, that the weights pursued a perfectly normal course, that the animals remained lively and healthy, and that pairs selected at random bred in a normal manner with an average number of healthy young. The results are given in Table 3.

TABLE 3.—*Hemoglobin Concentration in Rat Group 1*

| On Iron-Free Diet | | | On Iron-Containing Diet | | |
|---|---|---|---|---|---|
| Rat | March 5 | September 24 | Rat | March 5 | September 24 |
| 2 | 1.031 | 1.190 | 1 | 1.081 | 1.205 |
| 4 | 1.000 | 1.095 | 3 | 1.141 | 1.058 |
| 6 | 1.082 | 1.068 | 5 | 1.073 | 1.162 |
| 8 | 1.101 | 0.974 | 7 | 1.021 | 1.146 |
| 10 | 1.167 | 1.153 | 11 | 1.148 | 1.187 |
| 12 | 1.018 | 1.098 | 13 | 1.127 | 1.215 |
| 14 | 1.023 | 1.213 | 15 | 1.032 | 1.199 |
| 16 | 1.086 | 1.066 | 17 | 1.050 | 1.213 |
| 18 | 1.044 | 1.078 | 19 | 1.101 | 1.127 |
| 20 | 0.950 | 1.002 | 21 | 1.090 | 1.078 |
| 22 | 1.024 | 1.041 | 23 | 1.062 | 1.092 |
| 24 | 1.161 | 1.157 | 25 | 1.122 | 1.135 |
| 26 | 1.031 | 1.093 | 27 | 1.048 | 1.015 |
| 28 | 1.124 | 0.834 | 29 | 1.103 | 1.031 |
| 30 | 1.182 | 1.090 | 31 | 1.103 | 1.244 |
| 38 | 1.109 | 1.142 | 33 | 1.063 | 1.092 |
| 40 | 1.134 | 1.063 | 35 | 1.077 | 1.017 |
| 40B | 0.923 | 1.125 | 37 | 1.062 | 1.076 |
| 42 | 1.100 | 1.166 | 40A | 1.156 | 1.037 |
| 44 | 1.093 | 1.088 | 41 | 1.103 | 1.059 |
| 46 | 1.148 | 1.244 | 43 | 1.097 | 1.093 |
| 48 | 1.075 | 1.129 | 45 | 1.045 | 0.996 |
| | | | 49 | 1.019 | 1.361 |
| Average | 1.073 | 1.098 | Average | 1.083 | 1.123 |

TABLE 4.—*Averages in Group 1*

| | |
|---|---|
| Iron-free diet | 75.5 mg. per kilogram of body weight |
| Iron diet | 87.1 mg. per kilogram of body weight |

It will thus be seen that while each group gained one or two points in hemoglobin concentration, the differences are well within the limits of natural variation and experimental error. After the last determination, the rats were killed, the entire digestive tract was removed, and the iron content of the entire rat determined by the method described. The average results of the iron analyses are given in Table 4.

We see, therefore, that while the bodies of the rats that received iron contained more iron than the controls on an iron-free diet, this in nowise affected the hemoglobin concentration. The iron is stored in the body, but seems not to be capable of conversion into hemoglobin, nor does it in any way stimulate the production or mobilization of iron from any possible reserve supply that may exist.

RAT GROUP 2 (THIRTY-SIX RATS)

In this group the experimental conditions that we had in Group 1 were repeated. The animals were kept on their respective diets four and one-half months.

A study of Table 5 shows that the group on an iron-free diet had a hemoglobin concentration of 1.061 at the beginning and 1.05 at the end of the experiment, while the group on an iron-containing diet had concentrations of 1.105 and 1.106 at these times. In other words, the changes in both groups were negligible in amount.

In this group, as in Group 1, we have the same increase in total body iron. It would seem evident that the iron must remain in the body for

TABLE 5.—*Hemoglobin Concentration in Rat Group 2*

| On Iron-Free Diet | | | On Iron-Containing Diet | | |
|---|---|---|---|---|---|
| Rat | May 3 | September 21 | Rat | May 3 | September 21 |
| 51 | 1.055 | 1.184 | 50 | 1.123 | 1.170 |
| 55 | 1.111 | 1.025 | 52 | 1.152 | 1.093 |
| 57 | 1.152 | 0.978 | 54 | 1.110 | 1.138 |
| 59 | 1.131 | 1.144 | 56 | 1.228 | 1.187 |
| 61 | 1.215 | 1.230 | 58 | 1.113 | 1.114 |
| 65 | 1.110 | 1.006 | 60 | 0.970 | 1.049 |
| 69 | 1.087 | 1.038 | 64 | 1.183 | 1.032 |
| 71 | 0.985 | 1.046 | 66 | 1.242 | 1.111 |
| 73 | 1.087 | 1.118 | 68 | 1.167 | 1.220 |
| 75 | 1.110 | 1.005 | 70 | 1.160 | 1.177 |
| 77 | 0.764 | 0.872 | 74 | 1.063 | 1.117 |
| 83 | 0.982 | 0.968 | 76 | 1.111 | 1.018 |
| 91 | 1.071 | 0.853 | 82 | 1.078 | 1.073 |
| 93 | 1.000 | 1.046 | 86 | 1.041 | 1.117 |
| 95 | 0.995 | 0.944 | 90 | 1.052 | 1.043 |
| 97 | 1.008 | 1.062 | 92 | 1.101 | 1.150 |
| 99 | 1.083 | 1.296 | 94 | 1.051 | 1.124 |
| | | | 96 | 1.085 | 1.130 |
| | | | 98 | 0.971 | 1.132 |
| Average | 1.061 | 1.060 | Average | 1.105 | 1.106 |

TABLE 6.—*Averages in Iron Analyses in Group 2*

| | |
|---|---|
| Iron diet | 73.6 mg. per kilogram of body weight |
| Iron-free diet | 59.5 mg. per kilogram of body weight |

some time, since the increase is much too great to be accounted for except on that assumption.

RAT GROUP 3 (EIGHTY-FIVE RATS)

As in the two previous groups, the rats were kept on the two diets for a little over four months. These rats were chosen as young as they could be handled successfully, i. e., about three or four weeks after weaning. At this time, as in the human infant after the second year, the normal hemoglobin curve is rising.

It will be seen that both groups gained in hemoglobin concentration in the normal manner and that the averages are almost identical.

The rats receiving iron gained 0.9, and the controls on an iron-free diet gained 0.1. Here, again, in young animals the oral administration of

iron fails to increase the rate of gain in the slightest degree. The large number of healthy young rats used makes an average of considerable accuracy.

After the last analysis, the rats were killed and the livers and spleens analyzed with the results given in Table 8.

TABLE 7.—*Hemoglobin Concentration in Rat Group 3*

| On Iron-Free Diet | | | On Iron-Containing Diet | | |
|---|---|---|---|---|---|
| Rat | June 5 | October 10 | Rat | June 5 | October 10 |
| 101 | 0.999 | 1.159 | 100 | 1.100 | 1.046 |
| 103 | 1.001 | 1.148 | 102 | 1.086 | 1.068 |
| 105 | 1.138 | 1.180 | 104 | 1.081 | 1.065 |
| 107 | 1.036 | 1.081 | 106 | 1.010 | 1.041 |
| 110B | 0.957 | 1.008 | 108 | 1.034 | 1.058 |
| 111 | 1.019 | 1.018 | 110 | 0.987 | 1.026 |
| 113 | 0.979 | 1.076 | 110A | 0.983 | 0.948 |
| 115 | 1.008 | 1.044 | 112 | 0.964 | 1.021 |
| 117 | 0.958 | 1.075 | 114 | 1.067 | 1.068 |
| 119 | 0.986 | 1.068 | 116 | 1.056 | 1.053 |
| 121 | 0.964 | 1.103 | 118 | 1.027 | 1.041 |
| 125 | 1.063 | 1.045 | 124 | 0.968 | 1.190 |
| 127 | 0.985 | 1.272 | 132 | 0.975 | 1.116 |
| 131 | 1.035 | 1.133 | 136 | 1.021 | 1.146 |
| 135 | 0.933 | 1.206 | 140 | 0.986 | 1.066 |
| 141 | 1.001 | 1.001 | 140A | 1.130 | 1.127 |
| 143 | 0.949 | 1.061 | 142 | 1.031 | 1.114 |
| 145 | 1.052 | 1.309 | 144 | 0.983 | 1.263 |
| 147 | 1.001 | 1.177 | 146 | 1.000 | 1.125 |
| 149 | 1.044 | 1.419 | 148 | 1.111 | 1.100 |
| 150B | 0.977 | 1.073 | 150 | 0.912 | 1.083 |
| 151 | 0.959 | 1.098 | 150A | 0.934 | 1.088 |
| 153 | 0.924 | 1.138 | 150C | 0.983 | 1.194 |
| 155 | 0.902 | 1.044 | 152 | 1.071 | 1.146 |
| 157 | 0.970 | 1.165 | 154 | 0.895 | 0.820 |
| 160B | 1.071 | 1.098 | 156 | 1.020 | 1.170 |
| 160C | 0.999 | 1.144 | 158 | 1.013 | 1.133 |
| 161 | 1.068 | 0.972 | 160 | 1.049 | 1.248 |
| 165 | 1.029 | 1.168 | 160A | 0.866 | 1.036 |
| 167 | 1.046 | 1.092 | 162 | 1.028 | 1.124 |
| 169 | 1.046 | 0.739 | 164 | 1.026 | 1.245 |
| 173 | 0.964 | 1.050 | 166 | 0.905 | 1.347 |
| 175 | 0.927 | 1.022 | 168 | 1.040 | 1.164 |
| 181 | 0.897 | 1.280 | 170 | 1.008 | 1.093 |
| 183 | 1.006 | 0.866 | 172 | 0.935 | 1.187 |
| 185 | 1.068 | 1.029 | 174 | 0.968 | 1.053 |
| 187 | 1.061 | 1.167 | 176 | 0.848 | 1.149 |
| 190B | 1.143 | 1.155 | 182 | 1.041 | 1.008 |
| 193 | 0.811 | 1.151 | 184 | 1.035 | 1.103 |
| 197 | 1.022 | 1.138 | 186 | 1.100 | 1.339 |
| 199 | 0.987 | 1.164 | 188 | 0.948 | 1.103 |
| | | | 190A | 1.148 | 1.177 |
| | | | 194 | 1.004 | 0.681 |
| | | | 196 | 1.067 | 1.048 |
| Average | 1.002 | 1.106 | Average | 1.012 | 1.100 |

TABLE 8.—*Averages in Iron Analyses in Group 3*

| Iron-Free Diet | | Iron Diet | |
|---|---|---|---|
| | Iron per 100 Gm. of Tissue | | Iron per 100 Gm. of Tissue |
| Livers | 28.0 mg. | Livers | 29.6 mg. |
| Spleens | 155.0 mg. | Spleens | 169.0 mg. |

These differences are relatively slight, and suggest that iron, in comparatively small quantities given in this way by mouth, while it remains in the body a considerable time, is not stored up in the liver and spleen in any great measure, probably owing to the fact that it is again excreted during the months the feeding is being carried on.

It is evident by comparison of these figures with those obtained for the iron content of the whole rat (in Groups 1 and 2) that some but not all of the iron is contained in the spleen and liver. A rat spleen averages 0.8, a liver 2.9, and the total blood about 6.2 mg. of iron.

RAT GROUP 4 (TWENTY-EIGHT RATS)

Young rats were bled (28 per cent. of their blood volume), then divided into two groups, one being placed on an iron-free and the other on an iron-containing diet. The hemoglobin concentration was estimated at short intervals. In less than eight weeks, the hemoglobin concentration of the blood had become stationary and was at the same level as previous to the bleeding. (To save space the original and intermediate

TABLE 9.—*Hemoglobin Concentration in Rat Group 4**

| Rats on Iron-Free Diet† | | | | Rats on Iron-Containing Diet‡ | | | |
|---|---|---|---|---|---|---|---|
| Rat | Feb. 25, 1924 | Feb. 27, 1924 | April 4, 1924 | Rat | Feb. 25, 1924 | Feb. 27, 1924 | April 4, 1924 |
| 1..... | 1.124 | Bled | 1.230 | 0..... | 1.093 | Bled | 1.015 |
| 3..... | 1.109 | (12 per | 1.083 | 2..... | 0.977 | (12 per | 1.160 |
| 5..... | 1.046 | cent.) | 1.168 | 6..... | 1.068 | cent.) | 1.199 |
| 9..... | 1.117 | | 1.133 | 14..... | 1.135 | | 1.193 |
| 11..... | 1.111 | | 1.174 | 18..... | 0.970 | | 1.141 |
| 15..... | 1.043 | | 1.177 | 20..... | 1.081 | | 1.188 |
| 19..... | 1.135 | | 1.119 | 24..... | 1.088 | | 1.073 |
| 21..... | 1.133 | | 1.068 | 26..... | 0.984 | | 1.038 |
| 23..... | 0.989 | | 1.151 | 30..... | 1.061 | | 1.072 |
| 25..... | 1.117 | | 1.132 | 32..... | 1.144 | | 1.149 |
| 31..... | 1.126 | | 1.166 | 36..... | 1.125 | | 1.080 |
| 33..... | 1.076 | | 1.083 | 44..... | 1.091 | | 1.129 |
| 35..... | 1.108 | | 1.152 | | | | |
| 37..... | 1.114 | | 1.174 | Average.. | 1.151 | | 1.114 |
| 43..... | 1.076 | | 1.152 | | | | |
| 45..... | 1.134 | | 1.156 | | | | |
| Average.. | 1.103 | | 1.145 | | | | |

* When the rats were bled, they were first etherized, and the blood was then drawn directly from the heart. The blood volumes were estimated from the figures of Scott and Barcroft, i. e., 6.28 c.c. of blood per hundred grams of rat.

† Average hemoglobin concentration before bleeding, 1.117. Rats first bled (28 per cent.) Nov. 27, 1923.

‡ Average hemoglobin concentration before bleeding, 1.113. Rats first bled (28 per cent.) Nov. 27, 1923.

readings are not given in Table 9.) The original average in the iron-free group was 1.117, and in the iron group, 1.113. The rats were then bled (12 per cent. of the blood volume) and a hemoglobin determination was made. Five weeks later the hemoglobin had again attained its original value. A glance at Table 6 shows that after the first bleeding the hemoglobin concentrations were identical in the two groups, the figures being 1.103 and 1.151. Five weeks after the second bleeding the same statement held true; the concentrations were 1.145 and 1.114. The group receiving iron in the diet was, if anything, a trifle lower, the rats on an iron-free diet gaining 0.04, those on an iron-containing diet losing 0.04.

In this group the hemoglobin values were not in the least influenced by the administration of medicinal iron. It may be noted that under our

dietary conditions the rapidity with which the hemoglobin values of the blood regained their original values after bleeding was very much greater in the rat than in the dog. After the last determination the animals were killed, and the iron contents of the livers and spleens was determined.

The increase, even though small, in the amount of iron in the livers and spleens of the group receiving iron in the diet makes it clear that the fault lies not with the absorption of the iron but with its failure to be converted into hemoglobin. That the increase is relatively small in animals receiving iron in small quantities and by mouth is not strange,

TABLE 10.—*Averages in Iron Analyses in Group 4*

| Iron-Free Diet | | Iron Diet | |
|---|---|---|---|
| | Iron per 100 Gm. of Tissue | | Iron per 100 Gm. of Tissue |
| Livers | 48.4 mg. | Livers | 52.6 mg. |
| Spleens | 138.0 mg. | Spleens | 147.0 mg. |

TABLE 11.—*Hemoglobin Concentration in Rat Group 5 A (Forty-One Rats)*

| On Iron-Free Diet | | | | On Iron-Containing Diet | | | |
|---|---|---|---|---|---|---|---|
| Rat | Before Bleeding, March 11 | | June 5 | Rat | Before Bleeding, March 11 | | June 5 |
| 50 | 1.105 | Bled | 1.072 | 50A | 1.020 | Bled | 1.129 |
| 55 | 1.083 | twice, | 1.085 | 50B | 1.039 | twice, | 1.148 |
| 59 | 1.141 | 30 per | 1.013 | 52 | 1.226 | 30 per | 1.202 |
| 60A | 1.191 | cent. | 1.116 | 56 | 1.098 | cent. | 1.105 |
| 61 | 1.094 | March 17, | 1.110 | 58 | 1.203 | March 17, | 1.068 |
| 63 | 1.093 | and | 1.113 | 60 | 1.101 | and | 1.215 |
| 69 | 1.070 | 25 per | 0.929 | 60B | 1.090 | 25 per | 1.078 |
| 71 | 1.171 | cent. | 1.199 | 62 | 1.146 | cent. | 1.148 |
| 73 | 1.090 | May 5 | 1.117 | 64 | 1.135 | May 5 | 1.174 |
| 75 | 1.106 | | 1.076 | 66 | 1.088 | | 1.263 |
| 77 | 1.153 | | 0.829 | 68 | 1.083 | | 1.171 |
| 80A | 1.142 | | 1.113 | 74 | 1.185 | | 1.203 |
| 80D | 0.988 | | 0.936 | 76 | 1.206 | | 1.130 |
| 83 | 1.125 | | 1.009 | 78 | 1.223 | | 1.228 |
| 85 | 1.086 | | 0.942 | 80 | 1.167 | | 1.146 |
| 89 | 0.946 | | 1.117 | 88 | 1.072 | | 1.206 |
| 90A | 1.108 | | 1.129 | 90 | 1.174 | | 1.180 |
| 90E | 1.191 | | 1.083 | 90C | 1.137 | | 1.173 |
| 93 | 1.092 | | 1.050 | 90F | 1.063 | | 1.081 |
| 95 | 1.203 | | 1.080 | 94 | 1.106 | | 1.194 |
| | | | | 98 | 1.109 | | 0.972 |
| Average | 1.100 | | 1.060 | Average | 1.132 | | 1.153 |

since the amounts are small and the time during which it may be excreted relatively long, as compared with the large doses and shorter times of injection in the groups receiving iron subcutaneously.

RAT GROUP 5 (FORTY-ONE RATS)

In a group of forty-one rats, the hemoglobin concentration was first taken, following which 2 c.c. of blood was removed from the heart. As the average weight was 85 gm., this represented 30 per cent. of the total blood volume. Half the animals were placed on iron-free and the other half on an iron-containing diet, and approximately five weeks later the

hemoglobin concentration was again determined. The two groups were found to be substantially identical. To save space, these intermediate figures are omitted. The rats of the foregoing groups were then bled again (25 per cent. of the blood volume), since on reflection it seemed highly probable that the reserve stores of iron in the liver, spleen, etc., would hardly be exhausted by a single bleeding. Thus it might be thought that medicinal iron may not be absorbed and utilized when only a moderate degree of anemia exists, and the liver and spleen contain a more available form of iron; yet medicinal iron may be absorbed and utilized when a severe anemia exists and iron reserves of the liver and spleen are greatly depleted.

One month after the second bleeding when the hemoglobin was again determined, the group on an iron-free diet was found to be 0.04 lower than at the beginning (1.1 and 1.06), while in the group on an iron-containing diet, the figures were 1.132 and 1.53, respectively. In

TABLE 12.—*Hemoglobin Concentration in Rat Group 5 B (Twenty-Eight Rats)*

| On Iron-Free Diet | | | | On Iron-Containing Diet | | | |
|---|---|---|---|---|---|---|---|
| Rat | Before Bleeding, March 11 | | July 23 | Rat | Before Bleeding, March 11 | | July 23 |
| 55 | 1.083 | Bled | 1.146 | 50B | 1.039 | Bled | 1.127 |
| 59 | 1.141 | 28 per | 1.119 | 52 | 1.236 | 28 per | 1.135 |
| 67 | 1.122 | cent. | 1.144 | 56 | 1.008 | cent. | 1.119 |
| 69 | 1.070 | July 10; | 1.086 | 60 | 1.101 | July 10; | 1.062 |
| 71 | 1.171 | had | 1.093 | 60B | 1.090 | had | 1.046 |
| 73 | 1.000 | been | 1.111 | 62 | 1.146 | been | 1.174 |
| 75 | 1.106 | previ- | 1.109 | 64 | 1.135 | previ- | 1.090 |
| 77 | 1.153 | ously | 1.101 | 66 | 1.088 | ously | 1.106 |
| 80D | 0.988 | bled | 0.990 | 74 | 1.185 | bled | 1.101 |
| 83 | 1.125 | twice | 1.093 | 76 | 1.206 | twice | 1.166 |
| 85 | 1.086 | | 1.068 | 78 | 1.223 | | 1.073 |
| 90E | 1.191 | | 1.053 | 80 | 1.167 | | 1.051 |
| 95 | 1.206 | | 1.049 | 90 | 1.174 | | 1.101 |
| | | | | 90E | 1.137 | | 1.006 |
| Average | 1.118 | | 1.089 | 94 | 1.106 | | 1.063 |
| | | | | Average | 1.148 | | 1.095 |

other words, we may conclude that after two bleedings of considerable size the animals on a diet containing iron showed essentially the same hemoglobin values as the control group with no iron.

To check further this result, a third bleeding was performed (28 per cent. of the blood volume) on most of the rats, and the hemoglobin readings were taken two weeks later. As will be evident from Table 12, the last average readings are substantially identical in the two groups. In the group on an iron-free diet, the hemoglobin concentration was 1.118 before the first bleeding, and 1.089 after the last, while in the group receiving iron the corresponding figures are 1.148 and 1.095, respectively. From these figures it is evident that even after three bleedings, aggregating 62.2 per cent. of the blood volume, the hemoglobin in the blood regained its normal value within a few months, and that the administration of medicinal iron in nowise facilitated this recovery.

The rats were then killed and the iron content of the livers and spleens determined.

It will be seen that while the hemoglobin concentration remained practically unchanged the iron content of the livers and spleens, particularly the latter, showed a considerable increase. The iron was absorbed to a greater or less degree but not converted into hemoglobin.

TABLE 13.—*Averages in Iron Analyses in Group 5 B*

| Iron Diet | Iron per 100 Gm. of Tissue | Iron-Free Diet | Iron per 100 Gm. of Tissue |
|---|---|---|---|
| Livers | 41.0 mg. | Livers | 37.2 mg. |
| Spleens | 112.0 mg. | Spleens | 71.0 mg. |

TABLE 14.—*Hemoglobin Concentration in Rat Group 6*

| On Iron-Free Diet | | | On Iron-Free Diet Plus Iron Given Hypodermically | | |
|---|---|---|---|---|---|
| Rat | February 9 | March 15 | Rat | February 9 | March 15 |
| 0A | 1.044 | 1.056 | D | 0.964 | 1.008 |
| 0B | 1.046 | 0.994 | 1 | 1.171 | 1.080 |
| 0C | 1.223 | 1.143 | 3 | 1.004 | 1.101 |
| 4 | 1.155 | 1.010 | 5 | 0.963 | 1.138 |
| 6 | 1.025 | 0.938 | 7 | 1.032 | 0.961 |
| 8 | 0.992 | 1.049 | 9 | 0.989 | 0.995 |
| 9 | 0.989 | 0.995 | 10A | 0.938 | 1.015 |
| 10 | 1.090 | 1.060 | 10B | 1.050 | 1.049 |
| 10A | 1.096 | 1.149 | 10D | 0.969 | 1.031 |
| 10B | 1.028 | 1.008 | 10E | 1.096 | 1.028 |
| 10C | 1.077 | 1.190 | 11 | 1.004 | 1.010 |
| 10D | 1.046 | 1.152 | 14 | 1.075 | 0.992 |
| 10E | 1.071 | 1.092 | 15 | 1.034 | 1.018 |
| 21 | 1.031 | 1.125 | 16 | 1.051 | 1.051 |
| 22 | 1.010 | 1.056 | 18 | 1.001 | 1.055 |
| 23 | 1.053 | 1.138 | 19 | 1.013 | 1.108 |
| 24 | 1.010 | 1.092 | 30 | 0.970 | 1.020 |
| 25 | 1.021 | 1.111 | 30A | 1.073 | 1.020 |
| 26 | 1.049 | 1.135 | 30B | 1.000 | 0.940 |
| 27 | 1.049 | 1.145 | 30F | 1.033 | 0.940 |
| 28 | 1.034 | 1.051 | 31 | 1.078 | 1.044 |
| 29 | 1.096 | 1.097 | 33 | 1.093 | 1.028 |
| 40 | 1.027 | 0.947 | 35 | 0.981 | 1.033 |
| 40A | 1.083 | 1.174 | 36 | 1.102 | 1.091 |
| 40C | 0.961 | 1.063 | 37 | 1.156 | 0.947 |
| 40D | 1.039 | 1.043 | 38 | 0.956 | 1.006 |
| 40E | 1.043 | 1.098 | 39 | 1.041 | 1.066 |
| 41 | 1.018 | 1.025 | | | |
| 42 | 0.961 | 0.949 | Average | 1.031 | 1.030 |
| 43 | 0.965 | 1.077 | | | |
| 44 | 1.050 | 1.017 | | | |
| 45 | 1.045 | 1.086 | | | |
| 46 | 1.051 | 0.949 | | | |
| 47 | 1.038 | 1.247 | | | |
| 48 | 1.038 | 1.070 | | | |
| Average | 1.045 | 1.075 | | | |

RAT GROUP 6 (SIXTY-TWO RATS)

In Group 6 the intention was to test the value of medicinal iron used hypodermically. Young rats were chosen; their concentration was determined, and they were then divided into two groups, both on an iron-fee diet, but one group receiving 0.5 c.c. of a 1 per cent. solution of iron and ammonium citrate subcutaneously three times a week. These

diets and injections were continued for five weeks during which hemoglobin determinations were made several times. As the intervening determinations showed nothing of significance, only the first and last determinations are given in Table 14.

It is evident from an inspection of the figures in Table 14 that the group receiving injections remained exactly stationary at 1.031 and 1.03, while the control (noninjected) group gained a mere trifle, reaching 1.045 and 1.075. These results demonstrate that with all rats on an iron-free diet medicinal iron, hypodermically given, in nowise increases the hemoglobin concentration. As a matter of fact, we have shown in other rats that the long continued use of iron in this way and in this dose produces a distinct deleterious effect; the rats become sick, do not increase normally in weight, and many die.

TABLE 15.—*Averages in Iron Analyses in Rat Group 6*

| | Injected Rats | | Noninjected Rats | |
|---|---|---|---|---|
| | Iron per 100 Gm. of Tissue | | Iron per 100 Gm. of Tissue | |
| Livers | 71.6 mg. | Livers | 22.3 mg. | |
| Spleens | 105.0 mg. | Spleens | 85.2 mg. | |

TABLE 16.—*Comparative Hemoglobin Concentrations in Young of Rats on Iron-Free Diet and on Iron-Containing Diet*

| Dams on Iron-Free Diet | | Dams on Iron-Containing Diet: |
|---|---|---|
| Extinction Coefficient | Extinction Coefficient | Extinction Coefficient |
| 1.058 | 0.999 | 1.093 |
| 1.084 | 1.024 | 1.041 |
| 1.084 | 0.975 | 1.068 |
| 0.997 | 1.017 | 1.073 |
| 1.106 | 0.970 | 1.086 |
| 1.081 | 1.004 | 1.188 |
| 1.027 | 0.934 | 0.887 |
| 0.994 | 0.999 | 1.109 |
| | | 1.061 |
| Average | 1.022 | 1.059 |

After the last determination of hemoglobin, the animals were killed and the iron content of the livers and spleens was determined. The results are given in Table 15.

As might have been expected with relatively large doses given subcutaneously, the storage in the liver and spleen was very great, yet there was not the slightest evidence of its utilization as hemoglobin.

### RAT GROUP 7 (SIXTY-ONE RATS)

In this group an attempt was made to determine whether the young of rats that had been kept on an iron-free diet during the entire period of gestation and lactation would have a lower hemoglobin concentration than those born of dams that had been kept on such a diet plus medicinal iron during the same period.

To eliminate any possible effect of age, the blood was taken in all cases at about the twelfth day of life. In all, sixteen young from three dams on an iron-free diet and nine young from two dams on an iron-containing diet were studied. The results are shown in Table 16.

In view of the individual concentrations of hemoglobin, these results are essentially identical, or at least within the margin of variation found in different groups of animals. To make this point clear, we append a table of two groups of animals of exactly the same age whose dams were on a general mixed diet. As will be seen, the average of the first group is 1.061, that of the second 1.105, a difference of a little less than 4 per cent., which is approximately the difference between the two groups under discussion.

TABLE 17.—*Hemoglobin Concentrations in Animals on General Mixed Diet*

| Rat | Extinction Coefficient | Rat | Extinction Coefficient |
|---|---|---|---|
| 1 | 1.055 | 1 | 1.123 |
| 2 | 1.111 | 2 | 1.152 |
| 3 | 1.152 | 3 | 1.110 |
| 4 | 1.131 | 4 | 1.228 |
| 5 | 1.215 | 5 | 1.113 |
| 6 | 1.110 | 6 | 0.970 |
| 7 | 1.067 | 7 | 1.182 |
| 8 | 0.985 | 8 | 1.242 |
| 9 | 1.087 | 9 | 1.167 |
| 10 | 1.110 | 10 | 1.160 |
| 11 | 0.764 | 11 | 1.063 |
| 12 | 0.982 | 12 | 1.111 |
| 13 | 1.071 | 13 | 1.078 |
| 14 | 1.090 | 14 | 1.041 |
| 15 | 0.995 | 15 | 1.052 |
| 16 | 1.008 | 16 | 1.101 |
| 17 | 1.083 | 17 | 1.051 |
| | | 18 | 1.085 |
| Average | 1.061 | 19 | 0.971 |
| | | Average | 1.105 |

The conclusion would seem justified that the administration of medicinal iron to pregnant rats does not increase the hemoglobin concentration in the blood of the offspring.

## EXPERIMENTS ON DOGS

Healthy adult dogs were selected and placed on a maintenance diet of white bread and whole milk. This is a rather iron-poor, but by no means an iron-free diet, since milk contains, according to Sherman, 0.24 mg. of iron per hundred grams and white bread 0.90 mg. per hundred grams. In one group meat was added to test the difference of the behavior of the hemoglobin on the two diets. In this case half the bread was withdrawn, and an equal number of calories of meat were added. In other respects, the methods were essentially the same. Blood was obtained by a prick with a sharp cataract knife from the vein of the hind leg, and intravenous injections, when used, were given in the corresponding vein of the opposite leg. In all cases more than sufficient

time was allowed to elapse between successive hemoglobin determinations to permit the blood volume to return to the normal. Water was given freely and at all times.

Various authors have called attention to the fact that the dog is not a suitable animal for this type of work, a statement with which we are in entire accord. Our work is essentially based on the results of our rat experimentation, the dogs being used for intravenous injections, for which the rat is not suitable, and with the idea of forming a control in a different type of animal.

The dogs were made anemic by bleeding them from the heart, after etherization. The volume removed was calculated from the figures of Whipple, Robscheit and Hooper.

### DOG GROUP 1 (FIVE DOGS)

Large dogs were bled directly from the heart, the amount taken being 25 per cent. of the blood volume. In order to determine whether the anemia produced was actually as great as was postulated from the

TABLE 18.—*Hemoglobin Concentration in Dog Group 1*

| | Dog | Before Bleeding | October 24 | November 2 | November 15 | November 30 | December 12 |
|---|---|---|---|---|---|---|---|
| Noninjected controls | 4 | 1.046 | Bled 25 per cent. of blood volume | 0.783 | 1.067 | 1.015 | 0.949 |
| | 8 | 0.931 | | 0.654 | 1.098 | 0.970 | 0.970 |
| Average | | 0.989 | | 0.719 | 1.083 | 0.993 | 0.960 |
| Injected dogs | 3 | 1.119 | | ..... | 1.277 | 1.357 | 1.330 |
| | 5 | 1.236 | | ..... | 0.927 | 1.233 | 1.296 |
| | 7 | 1.251 | | ..... | 0.897 | 1.011 | 0.976 |
| Average | | 1.202 | | ..... | 1.034 | 1.204 | 1.201 |

amount of blood withdrawn, additional determinations of hemoglobin were made on two of the dogs, Nov. 2, 1923. The bleeding had been done, Oct. 24, 1923. The result were as follows: Before bleeding, the concentrations in the blood were 0.997 and 1.087, respectively, and on the second date 0.654 and 0.783, respectively. This is to be interpreted as showing that the blood volume had come back to approximately the normal, and also shows that the anemia, as measured by the concentration of hemoglobin, was approximately what it had been postulated to be. All the animals were on a bread and milk diet.

The figures given for Dogs 4 and 8 show that from October 24 to November 2 (nine days) the hemoglobin concentration was reduced from 0.989 to 0.719 (about 27 per cent.), showing that the blood volume was fully restored to normal in that time. We have made numerous similar observations. After a week or ten days, the regenerative effects are rapidly manifested. The figures for November 15 should be noted. The injected group received 1.5 c.c. of the iron and ammonium citrate. 1 per cent. solution, subcutaneously three times a week for five weeks.

It will be seen from an inspection of Table 18 that in the six weeks that elapsed from the date of bleeding the control dogs had regained their original hemoglobin concentrations. The injected animals showed no difference in the behavior of their blood from that shown by the noninjected controls, their concentration before bleeding being 1.202, and six weeks later 1.201.

We may conclude, therefore, that after a single large hemorrhage medicinal iron given subcutaneously does not enable the animal to regain a previous concentration of hemoglobin either more quickly or more efficiently.

At the end of the experiment the dogs were killed, and the amount of iron in the livers, spleens and bone marrows was determined. Table 18 shows the average figures obtained.

The great increase in the amount of iron in the spleens of the injected group is worthy of note. It is again evident that the failure to increase

TABLE 19.—*Averages in Iron Analyses in Dog Group 1*

| | Noninjected Controls | Injected Dogs |
|---|---|---|
| Livers | 25.5 mg. per 100 gm. of tissue | 30.0 mg. per 100 gm. of tissue |
| Spleens | 102.2 mg. per 100 gm. of tissue | 297.3 mg. per 100 gm. of tissue |

TABLE 20.—*Averages in Iron Analyses in Bone Marrow of Dogs*

| Noninjected Controls | | Injected Dogs | |
|---|---|---|---|
| Dog 4 | 514 | Dog 3 | 662 |
| Dog 8 | 564 | Dog 5 | 700 |
| | | Dog 7 | 681 |
| Average | 554 | Average | 681 |

Percentage of difference between averages, 22.9.

the concentration of hemoglobin is not due to any lack of iron, but to the inability of the body to convert iron into hemoglobin.

## IRON ANALYSES OF BONE MARROW

The two femurs of the dog were removed, sawed open, and the marrow removed, ashed and an iron determination made in the usual way on the ash. Table 20 shows the relation between the dogs' weight per kilogram of the dog and the amount of iron found in the marrow removed. Since the amount of iron is very small for simplicity the decimals are treated as whole numbers.

It was not feasible to examine all the bone marrow in the body, but we removed all the bone marrow in the two femurs, which are assumed to be proportional to the size of the dog and to constitute a fair average. It is evident from Table 20 that iron is stored in the bone marrow in the same way as in the liver and spleen.

DOG GROUP 2 (EIGHT DOGS)

Large dogs were bled 25 per cent. of the blood volume, the hemoglobin concentration having been determined shortly before. All the dogs were placed on the bread and milk diet. Six of the animals were given 1.5 c.c. of a 5 per cent. solution of iron and ammonium citrate, subcutaneously, every second day. The hemoglobin concentration was redetermined two and a half weeks later, at which time it was much lower in the injected group than in the normal noninjected controls. This suggested a distinctly toxic effect of the iron; so we reduced the dose to one fourth of that previously given, and continued the injections in other respects as before. At the end of one month, the control dogs had fully regained their original hemoglobin concentration, the injected animals being still far below their original figure. The exact figures

TABLE 21.—*Hemoglobin Concentration in Dog Group 2*

| | Dog | Before Bleeding, Jan. 30 | Jan. 30 | Feb. 11 | Feb. 18 | Feb. 25 |
|---|---|---|---|---|---|---|
| Noninjected controls | 1 | 1.403 | Bled 25 per cent. of blood volume | 1.156 | 1.228 | 1.386 |
| | 2 | 1.098 | | 1.046 | 1.103 | 1.213 |
| Average | | 1.250 | | 1.101 | 1.165 | 1.300 |
| Injected dogs | 4 | 1.213 | | 0.997 | 1.098 | 1.086 |
| | 5 | 1.034 | | 0.871 | 1.205 | 1.003 |
| | 6 | 1.255 | | 0.842 | 0.948 | 0.905 |
| | 7 | 1.180 | | 0.778 | 0.842 | 0.851 |
| | 8 | 1.274 | | 0.806 | 0.608 | 0.917 |
| | 9 | 1.233 | | 0.975 | 0.937 | 0.969 |
| Average | | 1.199 | | 0.898 | 0.939 | 0.955 |

TABLE 22.—*Averages in Iron Analyses in Dog Group 2*

| | Noninjected Controls | Injected Dogs |
|---|---|---|
| Livers | 26.4 mg. per 100 gm. of tissue | 49.1 mg. per 100 gm. of tissue |
| Spleens | 147.2 mg. per 100 gm. of tissue | 320.4 mg. per 100 gm. of tissue |

for the controls are 1.25 and 1.3 before bleeding and one month later, respectively. The corresponding figures for the injected animals are 1.199 and 0.955.

In this group of experiments, the dogs showed absolutely no advantage from the subcutaneous use of medicinal iron; it indicates quite clearly that a somewhat larger dose than the usual one is distinctly toxic.

The dogs were killed and their livers and spleens examined.

The relatively large amount of iron in the livers and spleens of the injected group is in striking contrast to the low figures for the hemoglobin concentration in the same group.

DOG GROUP 3 (EIGHT DOGS)

Dog Group 3 was intended to test the value of medicinal iron given intravenously after more or less complete exhaustion of the reserve iron

by repeated bleeding. The animals were kept on bread and milk, that is, an iron-poor diet. We proceeded as follows: The hemoglobin concentration was taken as usual, and then 25 per cent. of the calculated blood volume was removed. Ten days later another 25 per cent. was removed, and about five weeks later the hemoglobin concentration was again determined (intervening determinations were made, but to save space are not given in Table 22). Then for the third time 25 per cent. of the blood volume was removed, and following this three of the dogs were given intravenous injections of from 1 to 2 c.c. of a 1 per cent. solution of the double citrate of iron and ammonium three times a week. Both the injected and the control dogs were kept on the bread and milk diet throughout. The dose of iron given was approximately that given clinically to patients, taking into consideration the relative weights of man and dog. Seventeen and thirty-four days later hemoglobin concentrations were again taken. The results are shown in Table 23.

TABLE 23.—*Hemoglobin Concentration in Dog Group 3*

| Dog | Before Bleeding March 20 | Bled 25 per Cent. of Blood Volume March 27 | Bled 25 per Cent. of Blood Volume April 7 | May 13 | Bled 25 per Cent. of Blood Volume May 16 | June 2 | June 20 |
|---|---|---|---|---|---|---|---|
| 2 | 1.122 | On bread | On bread | 1.292 | Bread and | 1.081 | 1.166 |
| 3 | 1.067 | and milk | and milk | 1.206 | milk diet | 0.880 | 0.955 |
| 4 | 1.222 | diet | diet | 1.122 | plus intra- | 0.925 | 1.021 |
| Average | 1.137 | | | 1.207 | venous injection of iron | 0.902 | 1.047 |
| 5 | 1.145 | | | 1.163 | Bread | 1.032 | 1.061 |
| 6 | 1.208 | | | 1.174 | and milk | 0.961 | 1.060 |
| 1 | 1.177 | | | 1.233 | diet only | 1.063 | 1.163 |
| Average | 1.177 | | | 1.190 | | 1.019 | 1.095 |
| 8 | 0.944 | | | 0.864 | Placed on | 1.078 | 1.027 |
| 10 | 1.290 | | | 1.098 | partial meat diet | 1.081 | 1.267 |
| Average | 1.117 | | | 0.981 | | 1.080 | 1.147 |

It will be seen that the results are substantially identical. The injected animals had a hemoglobin concentration of 1.137 before the first bleeding, and the last determination showed 1.047. The noninjected controls had 1.177 before the first bleeding, and 1.095 at the last reading. If we prefer to compare the last reading with those taken just before the last removal of blood, May 16 (and this is probably more correct), the figures are essentially the same, except that the injected animals showed a somewhat greater diminution. We have noted the probable significance of this fact elsewhere.

As a further control two of the dogs, after the third bleeding, were placed on a partial meat diet having the same number of calories. The result was as follows: Before the third bleeding, the hemoglobin concentration was 0.981; on the last reading, one month later, 1.147. This shows the manner in which the blood responds to the ingestion of food

iron, since this group gained nearly 0.17 whereas the other two groups lost 0.16 and 0.10, respectively.

After the last hemoglobin determination, the dogs were killed and the iron content of their livers and spleens determined. The results are given in Table 24.

The much higher content of the livers and spleens in the group receiving iron intravenously is in striking contrast with the failure of the hemoglobin to increase beyond the figures for the noninjected controls. The great increase in iron in the animals receiving a partial meat diet is worthy of note. The last analyses show clearly the difference when food iron is fed.

DOG GROUP 4 (TWELVE DOGS)

In Dog Group 4 the reserve supply of iron in the liver, spleen, etc., was again greatly depleted by repeated bleedings, the animals being on the bread and milk, i. e., iron-poor diet. Twenty-five per cent. of the calculated blood volume was removed at each bleeding. The average iron-content was first determined on six of the dogs, and found to be

TABLE 24.—*Averages in Iron Analyses in Dog Group 3*

| | Milk Diet Only (Controls) | Milk Diet Plus Iron Injections | Milk Diet Plus Meat |
|---|---|---|---|
| Livers | 8.7 mg. per 100 gm. of tissue | 27.8 mg. per 100 gm. of tissue | 53.1 mg. per 100 gm. of tissue |
| Spleens | 118.7 mg. per 100 gm. of tissue | 643.1 mg. per 100 gm. of tissue | 461.2 mg. per 100 gm. of tissue |

27.3 mg. per hundred grams of tissue in the liver, and 118.6 gm. in the spleen.

Four of the dogs were bled at intervals of about ten days, this being the time required to be sure that the blood volume returns to normal. At the beginning the average hemoglobin concentration was 1.182. One month after the fourth bleeding, the average hemoglobin concentration was 0.749. As 25 per cent. of the blood was removed at each bleeding and four bleedings were performed, only 32.2 per cent. of hemoglobin should remain in the circulating blood, if none had been thrown in from the reserves in the liver, spleen, etc., or had been taken with the food. It may be safely assumed that in twenty days that elapsed between bleedings the blood volume had been entirely restored, since we showed in Dog Group 1 that the blood volume returns to normal in between seven and ten days. If not, then *a fortiori* the percentage of blood removed was still greater. Now the average concentration before the first bleeding was 1.182 and sixteen days after the fourth bleeding 0.749, that is, 63.5 per cent. of the original concentration; so the difference between 32.2 per cent. and 63.5 per cent., i. e., 31.3 per cent., had been furnished from the reserve supply, if it could not be accounted

for by the iron contained in the bread and milk diet, which is by no means negligible. Moreover, it is possible that when a great strain, as in this case, is placed on the blood forming organs, food iron may be utilized to a greater degree than when such a strain does not exist.

Two additional dogs (Dogs 3 and 4), were treated in precisely the same way, except that after the last bleeding they were given 10 mg. of iron and ammonium citrate subcutaneously three times a week. The average hemoglobin concentration in this group before any bleeding was 1.262 and sixteen days after the last bleeding 0.652, i. e., 51 per cent. of the original hemoglobin concentration. This is actually 12 per cent. less than in the noninjected group.

TABLE 25.—*Hemoglobin Concentrations in Dog Group 4*

| | Before Bleeding March 31 | May 24 | June 11 | July 8 | July 15 | Aug. 1 |
|---|---|---|---|---|---|---|
| Noninjected Controls | | | | | | |
| Dogs 1, 2, 6, 9..... | 1.182 | Bled 25% | Bled 25% | Bled 25% | Bled 25% | 0.749 i. e., 63.5% of original |
| Injected Dogs | | | | | | |
| Dogs 3, 4..... | 1.262 | Bled 25% | Bled 25% | Bled 25% | Bled 25% | 0.652 i. e, 51% of original |

TABLE 26.—*Averages in Iron Analyses in Dog Group 4*

| Noninjected Controls | | Injected Group | |
|---|---|---|---|
| Livers | | Livers | |
| Dog 1..... | 34.0 mg. per 100 gm. of tissue | Dog 3..... | 79.6 mg. per 100 gm. of tissue |
| Dog 2..... | 28.1 mg. per 100 gm. of tissue | Dog 4..... | 83.0 mg. per 100 gm. of tissue |
| Dog 6..... | 38.5 mg. per 100 gm. of tissue | | |
| Dog 9..... | 42.2 mg. per 100 gm. of tissue | Average... | 81.3 |
| Average... | 36.2 | | |
| Noninjected Controls | | Injected Group | |
| Spleens | | Spleens | |
| Dog 1..... | 90.1 mg. per 100 gm. of tissue | Dog 3..... | 340.2 mg. per 100 gm. of tissue |
| Dog 2..... | 101.5 mg. per 100 gm. of tissue | Dog 4..... | 250.8 mg. per 100 gm. of tissue |
| Dog 6..... | 114.3 mg. per 100 gm. of tissue | | |
| Dog 9..... | 123.6 mg. per 100 gm. of tissue | Average... | 280.5 |
| Average.. | 107.7 | | |

The dogs were then killed and the analyses of the livers and spleens showed the results given in Table 26. In this group the figures for each dog are given separately, to indicate average variations. In all other groups, to save space, only the averages are given.

It was thus evident that while subcutaneous injections of iron given to animals in which over half the blood had been removed failed to increase the hemoglobin concentration, they did increase the iron content of both liver and spleen more than 100 per cent. In other words, even when there was an urgent need of hemoglobin in the circulating blood iron injections failed to increase it, and while the injected iron was stored up in the liver and spleen it was not capable of being con-

verted into hemoglobin under our experimental conditions. It might be argued that a longer period of injections might have produced an increase in the hemoglobin concentration, but this argument is shown to be invalid by the greatly increased iron content of liver and spleen; this shows that these organs had an abundance of iron to furnish to the blood if only the iron were capable of transformation into hemoglobin. It might be further argued that the entire iron reserve of the liver and spleen, etc., had not been exhausted. This may very well be true, but hemorrhages that remove between 65 and 70 per cent. of the blood volume are certainly comparable with very severe anemias, as seen clinically. Further, it seems certain that if iron cannot be converted into hemoglobin, except under a still greater strain on the blood forming organs than is produced by hemorrhages of this magnitude, it would be practically worthless as a remedy.

## CONCLUSIONS

1. Inorganic iron, whether given by mouth, subcutaneously or intravenously, is absorbed and may be found especially in the liver and spleen, but is not converted into hemoglobin.

2. Animals made anemic by one or several large bleedings do not recover any more rapidly when inorganic iron is given in any of these ways.

3. The efficiency of food iron is very pronounced, and animals on a diet containing food iron only recover very rapidly from hemorrhages that remove an amount of iron greater than exists in the entire body outside the blood.

4. In the light of the foregoing experiments, the administration of inorganic iron has no therapeutic value in anemia.

# VITAL CAPACITY IN A CITIZENS' MILITARY TRAINING CAMP*

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This study of the vital capacity of a number of students at an army summer training camp, the Citizens' Military Training Camp held at Camp Meade, Md., July, 1924, was planned with a threefold purpose:

1. To obtain accurate vital capacity estimations on a relatively large and homogeneous group of individuals. The need of further observations as an aid in arriving at some standard by which we might judge all individuals of a given class is certainly great; and the army, with its large and well organized summer training camps, offers a peculiarly good opportunity for studies of value in meeting this need.

2. To determine whether or not the improvement in general physical condition resulting from the training undergone is accompanied by a corresponding change (increase) in the vital capacity. This general physical improvement is abundantly evidenced by all other criteria at our disposal, and is scarcely subject to doubt from any quarter; and it would not only be of value to learn whether or not the vital capacity increased in keeping with it, but it might even be that the value of vital capacity estimations in general should stand or fall according as it does or does not so increase.

3. To determine, if possible, the value of the vital capacity estimation as a criterion of what we call "general physical fitness," as disclosed primarily by a thorough physical examination. Some such criterion, while of great importance from the general medical point of view, would have a peculiar and tremendous value for the military services, for the only present means of determining this physical fitness (i. e., by thorough physical examination) is not only expensive in money, time and energy, but admittedly allows of many failures and errors. And any readily applicable procedure which might, even roughly, separate the "fit" from the "unfit"—which might serve as a sort of yardstick for measuring or classifying the physical manhood of the country—would prove of inestimable military value, especially under the need of a general mobilization, such as arose in 1917.

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## GENERAL CONDITIONS AND TECHNIC OF STUDY

The subjects of the present study were all young white men, aged from 16 to 20 years, inclusive, and coming from the states of Pennsylvania, Maryland, Virginia and the District of Columbia. They were, in some degree, selected from the average run of young men, for, accompanying their applications for admission to the camp was the report of a physical examination made by a local physician (frequently a member of the Army Reserve), and this report was considered in approving applications. To this extent selection was operative: approved applicants were all presumably in average good health and condition. There was no other factor of selection concerned; the young men came from both urban and rural communities and from various occupations (most of them being students), and they are believed to represent fairly the healthy "normal" youths of their ages.

Since the vital capacity estimations were made as a part of routine physical examinations, the subjects were almost invariably quite nude; in the few cases in which this was not true, there was no clothing that might have interfered with maximal respiratory effort above the waist.

All observations were made on accurately calibrated spirometers of the ordinary water-seal type, quite delicately counterpoised, and mounted on special bases to permit ready transport about the camp. Two such spirometers were used.

No connection or joint had an internal diameter of less than 1 inch, except directly at the mouthpiece, where detachable nipples of heavy glass tubing having an internal diameter of ⅝ inch (1.5 cm.) were used. A large number of these glass nipples were mounted firmly in rubber stoppers, and the whole, being easily removable from the rubber inlet hose, was carefully washed in two changes of water and then in double strength Dobell's solution before being again used. These nipples were of a size readily covered and grasped by the lips; every effort was made to eliminate leakage, and it is believed that in no reading recorded was leakage a factor.

The volume scales on the spirometers were graduated to 20 c.c., and readings to the nearest 10 c.c. were readily made. All readings were made by one or the other of the writers, and great care was used throughout to obtain accuracy of the highest degree.

Each man submitted to test was instructed as to what was desired of him, and was then given three "chances" or "blows;" he was urged to make his maximal expiratory effort (following maximal inspiration) at each attempt, and was challenged on the second and third attempts to better his preceding reading. Furthermore, since every observation on every man tested was made in the presence of a number of his fellows, with a resultant spirit or atmosphere of keen rivalry, it is felt

that practically every reading does represent maximal effort at the particular time on the part of the man concerned. All readings were recorded, and the highest of the three efforts accepted as representing the man's maximal expiratory output. The type of expiration required was a sustained single blow, starting more or less gradually, and avoiding all semblance of a sudden or violent blast. It was found that the usual length of the expiratory effort was from about six to seven seconds.

As simple as the actual procedure was, it was found difficult in certain cases to obtain at first what was believed to be a truly maximal expiration; this was due, apparently, to a total lack of knowledge as to how to breathe. In such cases, special effort was exerted to obtain satisfactory results; and, while in most of these the effort was successful, in a few cases it was found impossible to get satisfactory results. The latter cases were not recorded or considered in the findings herein reported.

It was manifestly impossible to make observations on the more than 3,500 men who entered camp in the two days over which the physical examinations extended; but it was felt that, if chance alone governed the selection of subjects, and a sufficiently large group were examined, a truly representative cross-section of the whole would be obtained. Accordingly, the spirometers were set up in a room through which all the men passed on their way from the physical examining hall to the dressing room. There was a constantly passing stream of men, with a constantly available subject at hand. The assistant of the operator of each apparatus, on the completion of an observation on one man, simply "tagged" the man nearest him in the passing line, who became the next subject. This method was followed on the occasion of both the incoming and outgoing examinations. Thus, no element other than pure chance operated to influence the selection of subjects.

## COMMENT ON FINDINGS

1. *Normals Before and After Training.*—It is to be noted that the two series of observations, as made on 825 healthy young men before, and 443 after, training, are not made on the same men throughout. While there were 103 of these men who chanced to have observations made on them on both occasions, it was impossible to control this feature, and any discussion or conclusions presented herein regarding the effect of the training undergone on vital capacity in the normal are based on the acceptance of the respective groups as fairly representing cross-sections of the total group of young men at the respective times of observation.

Since there were 103 men examined on both occasions, and since the first group of 825 represents approximately 23.5 per cent. of the men accepted for the camp and the second group of 443 is slightly more

than 13 per cent. of the men who finished the camp, this assumption is not believed to be unfounded. Furthermore, it will be noted on comparing Tables 1 and 2 that the numbers of men in both the total and separate age groups in the former are uniformly approximately double the corresponding figures in the latter chart. This would seem conclusive evidence not only that the selection of these individuals for study was on each occasion directed by chance, but also that both groups are respectively representative of the camp totals before and after training.

TABLE 1.—*Data on Eight Hundred and Twenty-Five "Normal" Men Before Beginning Training*

| Age, Years | No. in Group | Height, Cms. | Weight, Kilograms | Body Surface, Sq. M. | Chest, Cm. | | | Average Actual Output, C.c. | Average Vital Capacity, C.c. Per Sq. M. Body Surface |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Inspiration | Expiration | Expansion | | |
| 16 | 114 | 171.2 | 59.3 | 1.69 | 88.1 | 80.5 | 7.6 | 4,128 | 2,437 |
| 17 | 406 | 171.2 | 59.8 | 1.70 | 88.4 | 80.8 | 7.6 | 4,104 | 2,413 |
| 18 | 167 | 172.7 | 62.1 | 1.74 | 90.7 | 82.3 | 8.4 | 4,397 | 2,527 |
| 19 | 90 | 171.7 | 63.0 | 1.74 | 91.9 | 84.3 | 7.6 | 4,360 | 2,504 |
| 20 | 48 | 171.0 | 63.2 | 1.74 | 91.4 | 83.3 | 8.1 | 4,229 | 2,467 |
| Average | 825 | 171.5 | 60.7 | 1.71 | 89.4 | 81.5 | 7.9 | 4,206 | 2,453 |

Table 1 shows the physical data gathered on 825 healthy young white men between 16 and 20 years of age, inclusive, at the opening of the training camp. These men were selected by chance (as described above) from a group of more than 3,500 similar young men; and as these data were obtained before beginning training, they represent what we might expect to find in the average young man of this type and these ages.

TABLE 2.—*Data on Four Hundred and Forty-Three "Normal" Men After Training*

| Age, Years | No. in Group | Height, Cm. | Weight, Kilograms | Body Surface, Sq. M. | Chest, Cm. | | | Average Actual Output, C.c. | Average Vital Capacity, C.c. Per Sq. M. Body Surface |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Inspiration | Expiration | Expansion | | |
| 16 | 60 | 170.8 | 59.1 | 1.69 | 88.9 | 80.8 | 8.1 | 4,292 | 2,533 |
| 17 | 222 | 171.5 | 60.1 | 1.70 | 89.2 | 81.3 | 7.9 | 4,396 | 2,577 |
| 18 | 88 | 172.3 | 62.8 | 1.73 | 91.2 | 83.3 | 7.9 | 4,606 | 2,641 |
| 19 | 51 | 172.9 | 64.5 | 1.77 | 92.2 | 84.1 | 8.1 | 4,764 | 2,694 |
| 20 | 22 | 173.8 | 62.3 | 1.75 | 91.2 | 83.1 | 8.1 | 4,619 | 2,636 |
| Average | 443 | 171.9 | 61.1 | 1.72 | 89.9 | 82.0 | 7.9 | 4,477 | 2,602 |

Table 2 shows similar data on 443 men similar to the preceding 825, at the close of the four weeks' training period. The conditions surrounding the observations made on the two occasions were identical in every respect except that these 443 men had just completed the prescribed course of training.

In both Tables 1 and 2 an additional column has been added, showing the "vital capacity per square meter of body surface." This calculation is of value (just as in basal metabolism calculations) in making comparisons between individuals or between different observations at different times on the same individual. There is no doubt in our minds that the body surface, as determined from the height-weight formula of Du Bois and Du Bois, is the physical characteristic to which the expiratory output can most correctly be referred for comparison, and this is the basis on which the calculations shown in these columns are made.

While the height and weight measurements were not made by us personally, these measurements were made under our observation and by individuals fully understanding the need for accuracy, and they are believed to be entirely accurate and reliable. On the other hand, it may be remarked that, as a result of our experience in this study, we feel that routine chest measurements are not only unreliable but worthless. These measurements were, however, recorded, and are included herewith simply to make the record complete.

TABLE 3.—*Comparison of Body Surface, Average Actual Output and Vital Capacity in Cubic Centimeters Per Square Meter of Body Surface for "Normal" Men Before and After Training (From Tables 1 and 2)*

| Age, Years | Time of Observation | No. in Group | Body Surface Sq. M. | Average Actual Output C.c. | Increase | | Average Vital Capacity, C.c. Per Sq. M. Body Surface | Increase | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | C.c. | Per Cent. | | C.c. Per Sq. M. Body Surface | Per Cent. |
| 16 | Before | 114 | 1.69 | 4,128 | ... | ... | 2,437 | ... | ... |
| | After | 60 | 1.69 | 4,292 | 164 | 4.0 | 2,533 | 96 | 3.9 |
| 17 | Before | 406 | 1.70 | 4,104 | ... | ... | 2,413 | ... | ... |
| | After | 222 | 1.70 | 4,386 | 282 | 7.1 | 2,577 | 164 | 6.8 |
| 18 | Before | 167 | 1.74 | 4,397 | ... | ... | 2,527 | ... | ... |
| | After | 88 | 1.73 | 4,606 | 209 | 4.8 | 2,641 | 114 | 4.5 |
| 19 | Before | 99 | 1.74 | 4,360 | ... | ... | 2,504 | ... | ... |
| | After | 51 | 1.77 | 4,764 | 404 | 9.3 | 2,694 | 190 | 7.6 |
| 20 | Before | 48 | 1.74 | 4,299 | ... | ... | 2,467 | ... | ... |
| | After | 22 | 1.75 | 4,619 | 320 | 7.4 | 2,636 | 169 | 6.9 |
| Average | Before | 825 | 1.71 | 4,206 | ... | ... | 2,453 | ... | ... |
| | After | 443 | 1.72 | 4,477 | 271 | 6.4 | 2,602 | 149 | 6.1 |
| Appendix.—Similar averages for 103 normal individuals examined both before and after training. | | | | | | | | | |
| Average | Before | 103 | 1.73 | 4,308 | ... | ... | 2,481 | ... | ... |
| | After | 103 | 1.73 | 4,524 | 216 | 5.0 | 2,606 | 125 | 5.0 |

Table 3 brings together from Tables 1 and 2, for the several age groups, the body surface, volume output and vital capacity findings for the two observations before and after the training. It will be seen from this chart that every age group shows an increase in both actual expiratory output and in the calculated "cubic centimeters per square meter of body surface." The appendix to Table 3 presents the averages of the same data for the 103 men on whom observations were made at both

the beginning and the close of camp. It will be seen from the figures given that the increase in actual volume output as a result of the training amounted to 5 per cent. for these 103 men as against the 6.4 per cent. for the larger corresponding groups covered in Table 3, while the vital capacity in terms of cubic centimeters per square meter of body surface also increased by 5 per cent. for the 103 men as opposed to the 6.1 per cent. shown by the larger corresponding groups.

This increase of 5 per cent. in both actual volume output and vital capacity for these 103 men is slightly less than the corresponding increases shown by the larger groups of 825 and 443 men; but, accepting the latter figures as being more accurate because of the larger numbers concerned, it is evident that these increases approximate from 5 to 6.4 per cent.

As to whether the amount of this increase is of great significance or not, we cannot say. There is no comparable work reported in the literature, and these findings are presented for what they may be worth and with the hope that others may check them.

The data obtained at Camp Meade have been analyzed in numerous ways, and certain observations may be worth recording at this point. A comparison of Tables 1 and 2 will show that there was no change of any moment as a result of the training in either height, weight, body surface or chest measurements; the increase in actual expiratory output and vital capacity has already been discussed.

The sequence of the volumes of the expiratory efforts was tabulated, and it was found that, of the 825 men examined previous to training, 14.8 per cent. made their maximal effort on the first "blow," 23.9 per cent. on the second, and 61.3 per cent. on the third; while of the 443 men observed at the close of the training period, 14.2 per cent. made their maximal effort on the first attempt, 27.1 per cent. on the second, and 58.7 per cent. on the third. These figures show close agreement for the two groups in this respect; it is evident that the training did not influence the position in the three attempts of the maximal effort, and that, in routine vital capacity estimations on young men, we can expect about 15 per cent. to reach their maximal output on the first effort, 25 per cent. on the second, and 60 per cent. on the third. No relation between the type of individual and this sequence is discernible, and no explanation for these facts is available.

While there are no figures to support the observation, it is very definitely the opinion of both of us that youths of the "long waisted" type gave uniformly (and frequently markedly) higher readings than did those of approximately the same height but shorter chest conformation.

Many of these youths of slender stature and with comparatively small actual chest measurements far surpassed in expiratory volume those with much greater actual chest measurement but of shorter thoracic length.

This fact soon became striking while making the actual observations with the spirometers, and it early became evident that, for youths of approximately a given height (disregarding entirely the anteroposterior and lateral diameters of the chest) the expiratory output was at least roughly proportional to the length of the thorax. Whether or not this was due to a difference in potential mobility of the chest walls, or perhaps to the relative degrees of thoracic and abdominal breathing, cannot be said. Neither can we speak with regard to comparative actual lung capacity (as opposed to expiratory output) in these men; but it would seem certain that we can expect from the slender, long waisted type of young man a definitely greater maximal expiratory output than from the youth of approximately the same height but of shorter thoracic length.

2. *Group Below Par on Physical Examination.*—The purpose of this section of the article is to compare with the results on a normal and "physically fit" group of young men, as presented in the preceding section, the findings on another group of similar young men, of corresponding ages and examined in like manner, but found, on physical examination, "unfit" for full military duty.

This second group of young men, found to be either generally "below par" or subject to some abnormality, in either case sufficient to prevent their (at least immediately) undertaking full military duty, were assigned together in a "Special Training Company," and their training program, especially for about the first two weeks, differed somewhat from that which was routine for the camp at large. There was no serious organic defect or disease among them; they were separated from the other students because it was felt that they would be unable to stand the training pace set for the rest of the camp, and that they would probably prove something of a hindrance in any regular training company to which they might be assigned. There was the further idea underlying the formation of this company of determining what could be done, by means of a specially devised and carefully regulated and graduated system of training, toward bringing these youths up to the average standard of the camp.

The causes for assignment to this special company of the 115 men studied are listed on the next page. The conditions named are exceedingly abbreviated summaries of the findings reported by the examining medical officers.

| | | | |
|---|---|---|---|
| Underweight only | | 87 | 87 |
| Underweight with | Defective vision | 5 | |
| | Goiter | 1 | |
| | Varicocele | 1 | |
| | Flatfeet | 1 | |
| | Defective teeth | 1 | |
| | Short leg | 1 | 10 |
| Cardiac conditions | Pulmonic murmur, systolic function | 2 | |
| | Mitral insufficiency, well compensated | 1 | |
| | Mitral murmur, systolic | 1 | |
| | Apical murmur, systolic, not transmitted | 2 | |
| | Apical murmur, transmitted from left to right | 1 | |
| | Apical murmur, systolic, functional | 2 | |
| | Cardiorespiratory murmur, apical | 2 | |
| | Rapid heart with apical cardiorespiratory murmur | 1 | |
| | Rapid, irritable heart | 1 | 13 |
| Flatfeet only | | 2 | 2 |
| Spinal curvature, slight | | 2 | 2 |
| Unequal pupils, old, traumatic | | 1 | 1 |
| | | | 115 |

It will be seen from the foregoing data that ninety-seven (84 per cent.) of the 115 men were underweight according to the army's age-height-weight table of requirements, and it may be remarked that, in practically every case, the degree of underweight was such as to be manifest on casual inspection.

This condition was the primary one concerned in the formation of the special company, and it was the controlling factor in the training schedule outlined for the company.

That there was a distinct physical inferiority manifested by the men assigned to this company is definitely borne out by their subsequent records in the so-called "physical efficiency test," which is coming into more or less general use among schools and colleges. This test consists of the bar vault, high jump, broad jump and 100-yard dash, and certain arbitrary values are assigned to each for different ages. Under this test, according to the company commander's report, the Special Training Company's average was 39, while the students in the camp at large averaged 50.5.

With regard to the special handling of these men, they were, in the first place, under the constant and detailed supervision of a medical officer, and the line officers in charge of the company were all selected for their aptitude for the purpose in question. For the first eight days, drills started one-half hour later than for the other students, this time being spent by the men in their barracks, undergoing inspection, or at lectures by the medical officer, etc. After this eight day period, their drills began at the time routine for the camp. Throughout their four weeks of training, they had a half-hour rest period from 9:30 to 10 a. m., and again from 3:30 to 4 p. m., each day, during both of which periods a lunch consisting of 1 pint of milk and graham or similar crackers was served. This lunch was in addition to the regular meals served at the usual mess hours.

Regarding the diet of these men, the company commander, in his report to the commanding general of the camp, says:

> The diet consisted of the same meals as were provided the other citizens military training camp companies except that coffee, condiments, certain vegetables (such as cucumbers) and pastries were eliminated, and such items as lemonade, cocoa, other fresh vegetables, eggs, custards, light desserts and milk were added. Milk with graham crackers or any other slightly sweet cookie were served at 9:30 a. m. and 3:30 p. m. These lunches were highly appreciated. Cool water was available, and at all times they were urged to drink large quantities. The men were encouraged to take considerable time in which to eat and were never hurried out of the mess hall.

In addition to the foregoing, much attention was paid to general hygiene of the person. As much time as possible was spent in the open, and active play, outdoor calisthenics and games were encouraged and participated in by all members of the company.

A complete study of the vital capacity before, during and on completion of training was made on thirty-eight men of this Special Training Company. The averages of the findings obtained on the four examinations are presented in Table 4.

TABLE 4.—*Averages for Thirty-Eight Men on Whom Four Observations Were Made, with Actual and Percentage Increases Resulting from the Training Undergone* *

| Date | Height, Cm. | Weight, Kilograms | Body Surface, Sq. M. | Chest, Cms. | | | Average Actual Output, C.c. | Average Vital Capacity, C.c. Per Sq. M. Body Surface |
|---|---|---|---|---|---|---|---|---|
| | | | | Inspiration | Expiration | Expansion | | |
| July 1 | 165.4 | 49.6 | 1.53 | 83.1 | 75.7 | 7.4 | 3,566 | 2,344 |
| July 10 | 165.4 | 49.8 | 1.54 | 78.0 | 70.6 | 7.4 | 3,721 | 2,416 |
| July 18 | 165.4 | 50.4 | 1.54 | 80.0 | 71.9 | 8.1 | 3,742 | 2,428 |
| July 24 | 165.4 | 50.8 | 1.55 | .... | .... | ... | 3,820 | 2,470 |
| Increase | 0 | 1.2 | 0.02 | .... | .... | ... | 227 | 126 |
| Per cent. | 0 | 2.4 | 1.3 | .... | .... | ... | 6.3 | 5.4 |
| Appendix.—Same averages for three observations on 115 men of Special Training Company, the last being on completion of the training program. Presented as evidence that data given above for thirty-eight men are truly representative of the 115. There is remarkable agreement between figures for corresponding dates. | | | | | | | | |
| July 10 | 165.4 | 50.0 | 1.54 | 78.5 | 71.4 | 7.1 | 3,732 | 2,419 |
| July 18 | 165.6 | 50.4 | 1.54 | 78.7 | 71.1 | 7.9 | 3,740 | 2,424 |
| July 24 | 165.4 | 51.0 | 1.55 | .... | .... | ... | 3,858 | 2,479 |

* The first observation was made before beginning, and the last on completion of, the training program.

The number of men so studied is admittedly small, but three subsequent observations in this "below par" group included 115 men. The results of these three examinations are given in the appendix to Table 4. The latter figures, in their remarkable agreement with those of Table 4 proper for the corresponding examinations on the thirty-eight men, are presented as evidence justifying the contention that the figures for the thirty-eight men are not only representative of the larger group of 115, but also should be accorded the weight of the larger number in drawing conclusions as to the effect of the training on them. This the writers have done, and in comparing this special company with the camp at

large, and in drawing conclusions as to the effect of the training on the two groups, the findings on these thirty-eight men have been accepted as being truly representative of the entire special company.

It will be seen from a study of the several tables that every recorded observation on the "below par" group (with the possible exception of chest expansion) is definitely lower than the corresponding figures for the "normals."

The differences, before training, for body surface, actual expiratory output and vital capacity in terms of cubic centimeters per square meter of body surface are shown in Table 5 A, while a similar comparison following training is given in B of the same table.

From these comparative tabulations, it will be seen that the average actual expiratory output of the Special Training Company was slightly less than 15 per cent. below the "normal" at both the beginning and the conclusion of training; while the vital capacity of the special company,

TABLE 5.—*Comparison of Body Surface, Average Actual Output and Vital Capacity in Cubic Centimeters Per Square Meter of Body Surface, for "Normal" and "Below Par" Groups Before Beginning Training*

| | Body Surface, Sq. M. | Average Actual Output, C.c. | Difference (Below Normal) C.c. | Difference (Below Normal) Per Cent. | Average Vital Capacity, C.c. Per Sq. M. Body Surface | Difference (Below Normal) C.c. Per Sq. M. Body Surface | Difference (Below Normal) Per Cent. |
|---|---|---|---|---|---|---|---|
| | | A | | | | | |
| "Normals" | 1.71 | 4,206 | ... | .... | 2,453 | ... | ... |
| Special Training Company.. | 1.53 | 3,593 | 613 | 14.6 | 2,344 | 109 | 4.4 |
| | | B | | | | | |
| Same comparisons, for same groups as above, after training | | | | | | | |
| "Normals" | 1.72 | 4,477 | ... | .... | 2,602 | ... | ... |
| Special Training Company.. | 1.55 | 3,820 | 657 | 14.7 | 2,470 | 132 | 5.1 |

in terms of cubic centimeters per square meter of body surface, was below that of the "normals," by 4.4. per cent., before, and by 5.1 per cent. after, training. These facts force the conclusions, first, that while the men of the special company were definitely below the normal in both actual expiratory output and vital capacity both on beginning and at the completion of training, the differences between the two groups were approximately the same for both occasions; and, second, that the men of the special company were benefited by the training in roughly the same proportion as were the men in the camp at large.

The latter conclusion is borne out by a comparison of Table 4, which also shows the increases as a result of training for the special company, with Table 3 and its appendix, which present the same data for the camp at large. For the 103 "normal" individuals examined at both the beginning and the end of training, the increase in actual expiratory output and vital capacity were both 5 per cent.; for the large cross-section groups

of normals these increases were respectively 6.4 and 6.1 per cent. The increase for the Special Training Company lies in both cases between the preceding, being respectively 6.3 and 5.4 per cent.

## CONCLUSIONS

1. The actual maximal expiratory output of the class of normal white men covered by the study herein presented (aged from 16 to 20 years, inclusive, and coming from the states of Pennsylvania, Maryland, Virginia, and the District of Columbia) ranges from about 4,100 to about 4,400 c.c., with an average for the entire group of about 4,200 c.c.

2. The vital capacity in terms of cubic centimeters per square meter of body surface for the same group ranges from about 2,400 to about 2,500, with an average of approximately 2,450.

3. The course of training as prescribed in an army summer training camp results for all age groups concerned in an increase in both the maximal expiratory output and the vital capacity in terms of cubic centimeters per square meter of body surface. The increase in each is approximately from 5 to 6 per cent.

4. While the definite significance of this degree of increase in the vital capacity is not certain, the vital capacity does (to the degree shown) increase as the general physical condition of the individual improves.

5. The vital capacity of the young men adjudged "below par" on physical examination was, before training, definitely lower than that of the "normal," by 14.6 per cent. for the actual expiratory output, and by 4.4 per cent. for the output per square meter of body surface. These differences were practically unchanged by the training undergone, being respectively 14.7 and 5.1 per cent. at the end of camp.

6. While the significance of this amount of difference in vital capacity between the "fit" and the "unfit" is yet to be determined, the procedure is, at least to this degree, a measure of general physical fitness.

# THE EFFECT OF PHENOBARBITAL (LUMINAL) ON BLOOD PRESSURE IN ARTERIAL HYPERTENSION. III.

## A PRELIMINARY REPORT *

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The history of drug treatment in arterial hypertension has not been an encouraging one. Some of the commonly employed drugs that have enjoyed a certain degree of popularity at one time or another are: tinctures of aconite, veratrum viride and digitalis; potassium iodid and sodium iodid; the nitrites (nitroglycerin, sodium nitrite, erythrol tetranitrate); chloral hydrate; and the recently introduced benzyl esters, such as benzyl benzoate, benzyl acetate and benzyl mandelate. It appears therefore, rather an impertinence to report on yet another drug to be eulogized, tested, doubted and perhaps ultimately discarded.

In the outpatient department at Washington University School of Medicine, two patients were referred to us with arterial hypotension, one a girl, aged 19, suffering from epilepsy, the other an elderly man. The former had a systolic pressure of 88 mm. of mercury, the latter 104 mm. It was noted that both patients were taking phenobarbital (luminal) in fairly large doses. We then recalled that one of our hypertension patients had suffered from insomnia and had been given phenobarbital, 1½ grains (0.09 gm.) three times a day. Looking over his history and record sheet, we found that the week following the use of phenobarbital his systolic blood pressure had fallen from 250 to 190 mm. of mercury and his diastolic from 120 to 110 mm. Because of these chance observations phenobarbital was tested as to its value as a blood pressure lowering substance in arterial hypertension cases.

Phenobarbital (luminal) and sodium phenobarbital (luminal sodium) were first used in Germany in 1912 and have since been fairly widely employed both here and abroad in the treatment of epilepsy. As their value as hypnotics in insomnia, due to restlessness, and as sedatives in the treatment of epilepsy are well known, a review of these effects is not to be included in this article.

In 1912 Impens [1] first studied experimentally the pharmacology of phenobarbital and sodium phenobarbital. He determined the hypnotic

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1. Impens: Deutsch. med. Wchnschr. **38**:945, 1912.

and toxic doses of phenobarbital in the cat, dog and rabbit. He found from 25 to 30 mg. per kilogram in the cat, 40 to 50 mg. per kilogram in the dog and 80 mg. per kilogram in the rabbit necessary to produce sleep. This hypnotic dose was found to be one-fourth, one-third and one-half the toxic dose determined for the cat, dog and rabbit, respectively. Much larger doses were found to be necessary with sodium phenobarbital though the proportion to the toxic doses remained the same.

He found phenobarbital and sodium phenobarbital like most other hypnotics to reduce blood pressure. He cites three experiments on cats showing these drugs to produce a decrease in blood pressure. He states in his preface that the stage of reduction is often preceded by a period of increased pressure, "Eine Erhöhung des Blutdruches vor der Erniedrigung wird Zurveilen beobachted," and cites the following experiment: A 2,520 gm. cat had a control pressure of 130-137 mm. of mercury before the injection of 0.05 gm. per kilogram of sodium phenobarbital (luminal sodium) into the jugular vein. The time and blood pressures following the injection were:

| | | |
|---|---|---|
| 3 minutes, 90 mm. | 5 minutes, 134 mm. | 9 minutes, 146-153 mm. |
| 14 minutes, 145 mm. | 24 minutes, 151 mm. | 22 (or 32?) minutes, 148-166 mm. |
| 44 minutes, 124-150 mm. | 71 minutes, 112-140 mm. | 84 minutes, 114-130 mm. |

It will be seen that if a rise in blood pressure can be attributed to the drug in this experiment it must have occurred after the fall in blood pressure and not before.

He found the rate of respiration to be decreased but the depth increased by phenobarbital. Large doses produced respiratory paralysis, the heart continuing to beat some time longer. The kidneys were not damaged although part of the drug passed through them unchanged, the remaining portion being destroyed in the tissues. Wetzel [2] finds it possible to produce deep sleep in experimental animals with phenobarbital, without change in respiration and circulation.

Gruber and Baskett [3] noted that sodium phenobarbital and phenobarbital decrease the blood pressure in dogs, cats and rabbits when given intravenously, intraperitoneally or by mouth. They produce acceleration of respiration with decreased depth in small doses and respiratory paralysis with large doses only. The heart was noted to be slowed in rate, decreased in force of contraction and slightly dilated. The cutaneous and kidney blood vessels dilate simultaneously with a constriction of those of the spleen and loop of intestine. Perfusion experiments showed sodium phenobarbital to act peripherally and not centrally. The secretion of urine was not interfered with until the blood pressure became low.

2. Wetzel: Berl. klin. Wchnschr. **49**:937, 1912.
3. Gruber and Baskett: J. Pharmacol. & Exper. Therap. **30**:219, 1925; J. Lab. & Clin. Med. **10**:630, 1925.

Gregor [4] tested the side actions of phenobarbital (luminal) on the blood pressure in human beings. In eighty cases tested, he observed a fall in blood pressure with 0.2 gm. twelve hours after administration in two instances only. He employed 0.4 gm. each in seven women (Table 1).

It will be observed that failure of the drug to produce a fall in blood pressure occurred in one case only and that, the only hypertension case in the series.

Loewe [5] noted a fall in blood pressure after prolonged use of phenobarbital and considered this a side action of the drug.

Rissmann [6] and Miltner [7] report the use of phenobarbital in sixty cases of eclampsia, but give no data as to its value on blood pressure.

TABLE 1.—*Results of 0.4 Gm. of Phenobarbital (Luminal) in Seven Women (Gregor)*

| Blood Pressure Before | Blood Pressure 12 Hours Later |
|---|---|
| 150 - 92 | 126 - 84* |
| 124 - 82 | 104 - 73 |
| 142 - 80 | 130 - 88 |
| 184 - 100 | 188 - 102 |
| 124 - 67 | 114 - 74 |
| 144 - 100 | 114 - 74 |
| 140 - 90 | 130 - 86 |

* Later two attempts to reduce blood pressure failed.

Miltner does say, however, that it is valuable in this condition in that it lowers blood pressure and acts as a sedative to the respiratory system. He makes no further note as to how it affected the blood pressure in his cases, but states that venesection was resorted to in extreme cases. Since their observations, no one has recorded a fall in blood pressure, although over 2,000 cases have been reported on the use of phenobarbital in the treatment of epilepsy by Kino,[8] La Rue and Thornburgh,[9] Goldstein,[10] Dercum,[11] Kirk,[12] Raecke,[13] Austin,[14] Foley,[15] Fuchs,[16] Darling,[17]

4. Gregor: Therap. Monatsh. **36**:418, 1912.
5. Loewe: Deutsch. med. Wchnschr. **42**:947, 1912.
6. Rissmann: Med. Klin. **11**:427, 1915; Ztschr. f. Geburtsh. u. Gynäk. **40**:377, 1916; ibid. **41**:425, 1917.
7. Miltner, T.: Monatschr. f. Geburtsh. u. Gynäk. **53**:137, 1920.
8. Kino: Therap. d. Gegenw., September, 1912.
9. La Rue, F. G., and Thornburgh, H. T.: Kentucky M. J. **21**:681 (Dec.) 1923.
10. Goldstein: Deutsch. med. Wchnschr. **38**:987, 1912.
11. Dercum, F. X.: J. Nerv. & Ment. Dis. **1**:168, 1919; Therap. Gaz. **43**:609 (Sept.) 1919; J. Ment. Sc., July, 1914.
12. Kirk, C. C.: Am. J. Insan. **77**:559 (April) 1921; J. Arkansas M. Soc. **17**:128 (Nov.) 1920.
13. Raecke: Med. Klin. **8**:865, 1912.
14. Austin, M. L.: Ohio State M. J. **17**:683 (Oct.) 1921.
15. Foley: Institution Quart., Springfield, Ill., June 30, 1921.
16. Fuchs: Neurol. Centralbl. **33**:128, 1914.
17. Darling, I. A.: Arch. Neurol. & Psychiat. **9**:478 (April) 1923.

Galla,[18] Grinker,[19] Watkins,[20] Sands,[21] Small,[22] Hughes,[23] Hauptmann,[24] and others.

## METHOD

The method was practically the same as that used in studying the effect of benzyl benzoate on arterial hypertension.[25] In all instances the patients selected for this investigation had systolic blood pressures over 175 mm. of mercury at the beginning of observation. Some of the patients were the same ones previously reported on.[25] In all cases except one, the blood of these patients gave a negative Wassermann reaction. Except in the hospital cases, all the blood pressures were taken with the same mercury manometer. The maximum pressures were determined by the Korotkoff sounds [26] with a stethoscope. The fourth sound was taken as the diastolic pressure.

The ambulatory patients were seated near a desk in a quiet room. The left arm, from which the blood pressure readings were made, rested comfortably on the desk. Blood pressure readings were taken within two minutes after the patients had sat down and thereafter at ten minute intervals for twenty or more minutes. These pressures were then averaged to give the figures presented in Table 2. In all the observations the subjects were requested to sit as quietly as possible and not even to speak to the observer. In the hospital cases, the patients were kept in bed and the pressure taken while the patient was in the recumbent position. As nearly as possible the blood pressure readings were taken at the same hour each day. These were recorded for several days or even weeks until the control blood pressure level was established before the drug was prescribed. In the early observations readings were taken either every day or every other day, but later they were taken at weekly intervals. As nearly as possible, the patients were kept on a prescribed low protein diet.

All the ambulatory patients received 15 drops of a saturated aqueous solution of potassium iodid three times a day. Some of the patients received in addition 10 or 15 (depending on the size of patient) drops of tincture of digitalis three times a day. As long as the blood pressure was falling under this treatment and diet, phenobarbital was withheld.

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18. Galla: Brit. M. J. 2:320, 1921.
19. Grinker, J.: Experiences with Luminal in Epilepsy, J. A. M. A. **75**:588 (Aug. 28) 1920; Phenobarbital in Epilepsy, ibid. **79**:788 (Sept. 2) 1922.
20. Watkins, H. M.: New York M. J. **112**:891 (Dec. 4) 1920.
21. Sands, I. J.: Arch. Neurol. & Psychiat. **5**:305 (March) 1921.
22. Small, V. R.: Virginia M. Monthly **48**:386 (Oct.) 1921.
23. Hughes, W. N.: Rhode Island M. J. **4**:157 (Dec.) 1921.
24. Hauptmann: München. med. Wchnschr. **59**:1907, 1912.
25. Gruber, C. M., and Shackelford, H. H.: J. Lab. & Clin. Med. **9**:685 (July) 1924.
26. Erlanger, J.: Am. J. Physiol. **40**:86 (March) 1916; ibid. **55**:9 (Jan.) 1921.

TABLE 2.—*Summary of Laboratory Findings in Twenty-Seven Ambulatory Patients* *

| Case | Laboratory Findings: Blood: Nonprotein Nitrogen in Mg. per 100 C.c. Blood | Laboratory Findings: Blood: Percentage Phenolsulphonephthalein in 2 Hrs. | Laboratory Findings: Urine: Albumin | Laboratory Findings: Urine: Specific Gravity | Laboratory Findings: Urine: Casts | Blood Pressure on Admission | Blood Pressure After Routine Treatment and Diet: No. Days | Blood Pressure After Routine Treatment and Diet: Blood Pressure | Blood Pressure During Phenobarbital Treatment: No. Days | Blood Pressure During Phenobarbital Treatment: Blood Pressure | Blood Pressure After Phenobarbital Treatment: No. Days | Blood Pressure After Phenobarbital Treatment: Blood Pressure | Diagnosis and Remarks Concerning Toxic Condition During Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>White woman, aged 61 | 34.5 | 52 | 0 | 1.019 | Hyaline | 193-101 | 20 | 163- 94 | 4 | 139- 82 | 9 | 164- 90 | Arteriosclerosis; chronic infectious arthritis. Drowsy |
| 2<br>Colored woman, aged 68 | 24<br>33.4<br>33.3 | 30<br>39<br>36<br>42 | + | 1.004 to 1.015 | Hyaline | 230-121 | 20 | 219-115 | 6 | 171-103 | 7 | 215-110 | Chronic interstitial nephritis; cardiac decompensation; chronic myocarditis. Drowsy; "feels drunk"; pruritis |
| 3<br>White woman, aged 70 | 29<br>27.8<br>30.6 | 47<br>45<br>7<br>28<br>28<br>33<br>43 | Trace<br>3+ | 1.005 to 1.013 | Hyaline; granular | 224- 94 | 78 | 231- 98<br>233-106<br>230-104<br>249-109<br>239-112<br>243-108 | 5<br>4<br>7<br>3<br>10<br>16 | 175- 78<br>198- 84<br>185- 95<br>225-104<br>230- 97<br>226- 99 | 15<br>44<br>27<br>24<br>37 | 233-106<br>230-104<br>249-109<br>239-112<br>243-108 | Arteriosclerosis; chronic myocarditis; extrasystoles. "Uncertain feeling" |
| 4<br>Colored man, aged 50 | 62.5 | 15 | 3+ | 1.011 | Hyaline; granular | 208-132 | 13 | 215-130 | 8 | 214-131 | 28 | 224-133 | Chronic interstitial nephritis; uremia; duodenal ulcer; pyorrhea |
| 5<br>White man,† aged 58 | 34.3<br>33.9<br>25.0<br>30.3<br>33.3<br>37.2<br>31.2 | 42<br>54<br>53<br>52<br>41<br>30<br>45<br>36<br>32.7<br>43 | + | 1.009 to 1.026 | Hyaline; granular | 230-116 | 147 | 250-120<br>216-116<br>211-114<br>203-111<br>210-113<br>212-110<br>191-109<br>229-123 | 7<br>13<br>2<br>12<br>14<br>24<br>34<br>4 | 190- 90<br>182- 99<br>173-103<br>172-103<br>170- 95‡<br>176-100‡<br>172- 98§<br>193- 97 | 28<br>14<br>11<br>20<br>28<br>14<br>14 | 216-116<br>211-114<br>203-111<br>210-113<br>211-110<br>191-109<br>229-123 | Chronic interstitial nephritis; pulsus alternans; arteriosclerosis; old left hemiplegia. "Gait unsteady at times"; less nocturia |
| 6<br>White woman, aged 53 | 32.8<br>27.7 | 30<br>57<br>36 | + | .... | Hyaline; granular | 280-<br>240-120 | 11 | 265-119<br>234-112 | 6<br>1 | 205- 93<br>185- 86 | 12<br>18 | 232-100<br>227- 95 | Polyneuritis (diabetic); cardiac decompensation; pulsus alternans; hypertension (1916), 240-126; diabetes mellitus; arteriosclerosis |
| 7<br>White woman,† aged 43 | 27 | 42<br>58 | Very faint trace | 1.017 | Hyaline | 176-120 | 88 | 164-108 | 11 | 139- 95 | 7 | 143-101 | Chronic interstitial nephritis; old right hemiplegia |
| 8<br>White woman,† aged 48 | 25.6<br>23.3 | 39<br>30 | Very faint trace | 1.015 | 0 | 200-120 | 205 | 188-101<br>189-107 | 11<br>14 | 154- 89<br>174- 97§ | 17<br>24 | 177-104<br>199-102 | Mitral regurgitation; chronic myocarditis; chronic interstitial nephritis; hypertension since 1918, 200-120 |
| 9<br>Colored man,† aged 44 | 27.5<br>26.6<br>31.0 | 39<br>27<br>37 | + | 1.017 | 0 | 190-116 | 93 | 152-108 | 3 | 136- 91 | 13 | 150-103 | Pulmonary tuberculosis (arrested); chronic interstitial nephritis |
| 10<br>Colored woman, aged 50 | 37.5<br>37.7 | 57<br>45<br>35 | +<br>2+ | 1.006 to 1.008 | 0 | 228-110 | 63 | 224-109 | 25 | 181-100§ | 14 | 213-120 | Chronic interstitial nephritis; old right hemiplegia. Vertigo; sensation of falling backward |
| 11<br>Colored woman, Aged 44 | 41.7<br>25.9 | 42 | Trace | 1.010 | Hyaline | 240-125 | 112 | 257-118 | 5 | 209-118 | 23 | 243-127 | Chronic interstitial nephritis; old left hemiplegia; arteriosclerosis; vertigo; tendency to fall back |
| 12<br>White man,† aged 61 | 40<br>36<br>40.8 | 37<br>40<br>42 | Very faint trace | 1.015 | Hyaline | 207-105 | 68 | 207-105<br>194-104 | 4<br>3 | 169- 98‡<br>166- 97 | 6<br>10 | 194-104<br>205-112 | Chronic interstitial nephritis; inguinal hernia; arteriosclerosis. Tendency to fall back |
| 13 | 43.5 | 66 | 0 | 1.025 | 0 | 217-110 | 57 | 214-112 | 20 | 187-108 | 17 | 215-108 | Pulmonary tuberculosis (arrested); chronic interstitial nephritis. |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13<br>White woman,†<br>aged 42 | 43.5<br>40.8<br>35.4 | 66<br>35<br>27 | 0 | 1.025 | 0 | 217-110 | 57 | 211-112 | 29 | 187-108 | 17 | 215-108 | Pulmonary tuberculosis (arrested); chronic interstitial nephritis. Nervous |
| 14<br>Colored man,<br>aged 47 | 36<br>41.7<br>35.7<br>25.7 | 65<br>61<br>73<br>44 | Very faint trace | 1.014 to 1.025 | Hyaline; granular | 179-124 | 66 | 172-126 | 5 | 145-104 | 55 | 177-121 | Arteriosclerosis; old right hemiplegia; chronic interstitial nephritis; chronic prostatitis. Vertigo; pricking sensation of skin |
| 15<br>Colored woman,†<br>aged 27 | 32.5<br>34.4<br>35.7 | 59<br>48 | + | 1.004 to 1.017 | Hyaline | 250-155 | 78 | 229-177 | 10 | 226-168 | 2 | 266-198 | Nontoxic goiter; chronic interstitial nephritis |
| 16<br>Colored woman,†<br>aged 63 | 35<br>49<br>28.1 | 46<br>50<br>48 | + | 1.008 to 1.019 | 0 | 217-127 | 85 | 201-125 | 3 | 187-111 | 9 | 219-125 | Arteriosclerosis; chronic myocarditis |
| 17<br>White woman,<br>aged 66 | .... | 50 | Trace | 1.015 to 1.025 | 0 | 204-104 | 35 | 170- 78 | 4 | 137- 76 | 12 | 165- 81 | Arteriosclerosis; chronic myocarditis |
| 18<br>Colored woman,<br>aged 47 | 26.6 | 51 | + | 1.016 to 1.020 | 0 | 204-104 | 16 | 204-104 | 11 | 165- 94 | .. | ..... | Lupus erythematosis; chronic interstitial nephritis; constipation; pyorrhea. Drowsy |
| 19<br>White woman,<br>aged 60 | 32<br>29.4<br>32.8<br>34.4 | 51<br>16 (1 hr.)<br>38<br>29<br>22 (1 hr.) | Trace | 1.010 | 0 | 228-110 | 13 | 204-121<br>218-124<br>213-118<br>218-118 | 2<br>7<br>7<br>14<br>5 | 155- 95<br>182-114§<br>189-109§<br>183-108§<br>194-106 | 22<br>29<br>7 | 213-127<br>213-127<br>215-119 | Chronic interstitial nephritis. Drowsy |
| 20<br>White man,<br>aged 54 | 54<br>60.9 | 24<br>17<br>16 | 3+ | 1.011 to 1.015 | Hyaline; granular | 195-152 | 5 | 195-133<br>224-128 | 9<br>7 | 202-122<br>196-124* | 14<br>7 | 224-138<br>214-217 | Chronic interstitial nephritis; uremia (chronic); myocarditis (chronic); aortitis; cardiac decompensation |
| 21<br>Colored woman,<br>aged 59 | 25 | 44 | 0 | 1.028 | Hyaline | 190-110 | 83 | 144- 80 | 2<br>6 | 127- 73<br>132- 77 | 18 | 153- 85 | Arteriosclerosis; Parkinson's disease; pyorrhea. Drowsy |
| 22<br>Colored man,<br>aged 46 | 34.5 | 68 | .. | .... | ..... | 186- 89 | 6 | 170- 89 | 6 | 164- 79 | 13 | 176- 76 | Arteriosclerosis. Drowsy |
| 23<br>White man,<br>aged 69 | 27.8 | 39 | 2+ | 1.010 to 1.021 | Hyaline; granular | 200-116 | 24 | 191-105 | 24 | 169- 99§ | .. | ..... | Chronic interstitial nephritis; chronic myocarditis; arteriosclerosis; ichthyosis. Drowsy; tendency to fall back |
| 24<br>Colored man,<br>aged 54 | 33.4 | 29 | 3+ | 1.008 to 1.012 | Hyaline; granular | 250-160 | 16 | 206-118 | 5 | 168-105 | 7 | 194-116 | Pulsus alternans; chronic interstitial nephritis; cardiac decompensation; syphilis; late Wassermann reaction 4+ |
| 25<br>White woman,<br>aged 62 | 33.1 | 41<br>47 | 0 | .... | 0 | 199- 90 | 63 | 192- 89 | 7 | 169- 77§ | 12 | 177- 82 | Chronic gastritis (hyperchlorhydria). Drowsy |
| 26<br>Colored woman,<br>aged 48 | 20.8 | 34<br>44 | + | 1.015 | 0 | 230-130 | 7 | 218-126 | 7 | 177-103§ | 10 | 187-109 | Chronic interstitial nephritis |
| 27<br>White man,<br>aged 45 | 23.3 | 65 | Very faint trace | 1.018 | 0 | 217-129 | 100 | 220-110 | 14 | 175- 90 | 14 | 207-117 | Arteriosclerosis; chronic prostatitis |

* The blood pressure readings are given in millimeters of mercury. In all cases the average of the three ten minute blood pressure readings is given. The readings given in the column under routine treatment are those taken the day phenobarbital was administered. All the patients were ambulatory and were treated first with diet and with a saturated aqueous solution of potassium iodid, fifteen drops three times a day. Some were given tincture of digitalis, from 10 to 15 drops three times a day, depending on the size of the patient and the kidney involvement. Unless otherwise indicated, phenobarbital was given in 1.5 grain (0.09 gm.) doses three times a day. All patients gave a negative blood Wassermann reaction except Case 24.

† This and all following cases so indicated were reported on previously.[25] The case numbers are the same in each.

In this and the following cases so indicated ‡ = 0.75 grain (0.04 gm.) given three times a day; § = 1.5 grains (0.09 gm.) twice a day, morning and evening; # = 3 grains (0.19 gm.) three times a day; and * = 1.5 grains (0.09 gm.) four times a day.

Phenobarbital was not prescribed in larger doses than 1½ grains (0.09 gm.) three times a day. (In one case the patient took by mistake without ill effects 3 grains [0.19 gm.] three times a day for four days.) Smaller doses were given to some patients and to some 1½ grains (0.09 gm.) were given less frequently.

## RESULTS

Here, as in our previous article,[25] temporary rest alone caused a marked fall in blood pressure. In some patients the preliminary treatment of potassium iodid and digitalis markedly lowered the blood pressure.

TABLE 3.—*Effect of Phenobarbital on Blood Pressure in Patients with Arterial Hypertension at Rest in Bed* *

| Case | Blood Pressure on Admission to Hospital | Number of Days Rest in Bed | Blood Pressure After Rest in Bed | Number of Days Phenobarbital Was Given | Number of 1½ Grain (0.09 gm.) Doses a Day | Blood Pressure During Phenobarbital Treatment | Blood Pressure After Phenobarbital Was Discontinued | Diagnosis and Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 Age 46 | 273-128 | 9 | 246-134 | 3 | 3 | 208-128 | 224-112 | Myocarditis; chronic mitral insufficiency; caries of teeth; general arteriosclerosis; glaucoma; chronic interstitial nephritis; hypertrophy of heart |
| 2 Age 39 | 236-142 | 6 | 240-140 | 3 | 3 | 196-116 | 220-128 | Chronic interstitial nephritis; optic neuritis; caries of teeth; general arteriosclerosis; metastatic carcinoma of calvarium (osteoplastic); chronic tonsillitis, sphenoidal sinusitis |
| 3 Age 57 | 260-148 | 3 | 248-135 | 10 | 3 | 175-105 | ..... | |
| 4 Age 44 | 210-135 | 7 | 205-128<br>190-120 | 7 | 2<br>2 | 168-100<br>170-100 | 190-120 | Mitral regurgitation; cardiac hypertrophy; cardiac decompensation; chronic interstitial nephritis; erysipelas. The patient died suddenly |
| 5 Age 64 | 220-120 | 3 | 210-115 | 4 | 3 | 180-105 | 190-110 | Arteriosclerosis, general; chronic constipation |
| 6 Age 48 | 220-108 | 2 | 209-104 | 10 | 3 | 160- 90 | ..... | Mitral regurgitation; arteriosclerosis |
| 7 Age 60 | 240-150 | 8 | 220-145 | 21 | 3 | 175-120 | ..... | Arteriosclerosis; chronic infectious arthritis |
| 8 Age 54 | 210-148 | 4 | 204-140 | 4<br>6 | 3<br>1 | 170-120<br>160-110 | ..... | Arteriosclerosis; chronic interstitial nephritis |

* The blood Wasermann reaction was negative in all cases. All the patients were white women varying in age from 39 to 64 years.

The immediate results with phenobarbital on arterial hypertension were satisfactory. We have used this drug in the treatment of hypertension in twenty-seven ambulatory and eight hospital cases (Tables 2 and 3). In some instances use has been almost continuous for as long as eight months with beneficial results. In others the phenobarbital ceased to have an effect after three or four weeks' administration. In the ambulatory patients thus treated, a definite fall in arterial blood pressure was noted in twenty-three of the twenty-seven cases. In some

of these the drug was tested several times with the same results. In the four instances in which it was not effective, Cases 4, 15, 20 and 22, two of the patients appeared to have severe nephritis with cardiac decompensation. The blood nonprotein nitrogen was high and the urine contained large amounts of albumin. Cases 4 and 20 showed passive congestion of the lungs and liver, edema of the extremities, and no doubt there was a similar involvement of the kidneys. In addition, Case 4 was very obstinate and some doubt has arisen as to whether or not the patient had followed any part of the treatment outlined. Both

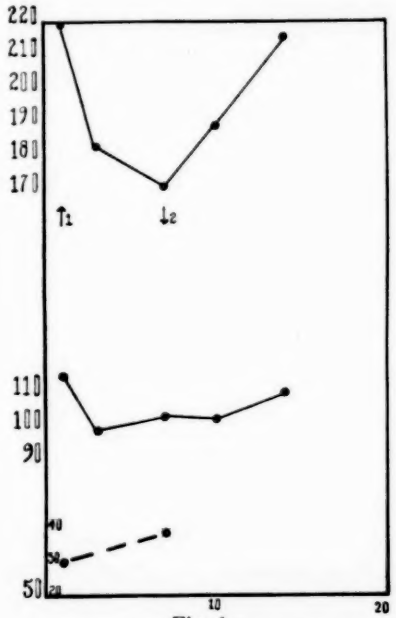


Fig. 1.

Fig. 1.—Curve plotted from the data obtained from Case 2, Table 2, a colored woman, aged 68. In this and the following figures, the blood pressure in millimeters of mercury and the percentage of phenolsulphonephthalein excretion for two hours are plotted on the ordinate, the former figures are to the left of the line, the latter to the right, and the time in days on the abscissa. The top record is the systolic blood pressure, the middle the diastolic, and the bottom record the phenolsulphonephthalein excretion. In all cases the average of the three (ten minute intervals) readings is plotted. 1, blood pressure on the day before phenobarbital, 1½ grains (0.09 gm.) three times a day was administered; 2, phenobarbital discontinued.

patients were recommended for hospital treatment, which Patient 4 declined. The third case was that of a colored woman, aged 27, Case 15. She had been treated in every way available in the dispensary

without beneficial results. In this case, nitroglycerin, 1/50 grain, caused a rise in blood pressure; sodium nitrite, benzyl benzoate, salt restriction, etc., had no effect.

In the twenty-three cases in which phenobarbital was effective, the fall in systolic pressure varied during the first series of administrations from 14 to 60 mm. of mercury, with an average of 35 mm. The fall in diastolic pressure varied from 0 to 30 mm. of mercury, with an average of 13 mm. (Table 2 and Charts 1 and 2). In order to conserve space in Table 2, the average readings are given, i. e., the average of the three readings taken on a single day. Although many blood pressure readings were made while the patient was under our observation and

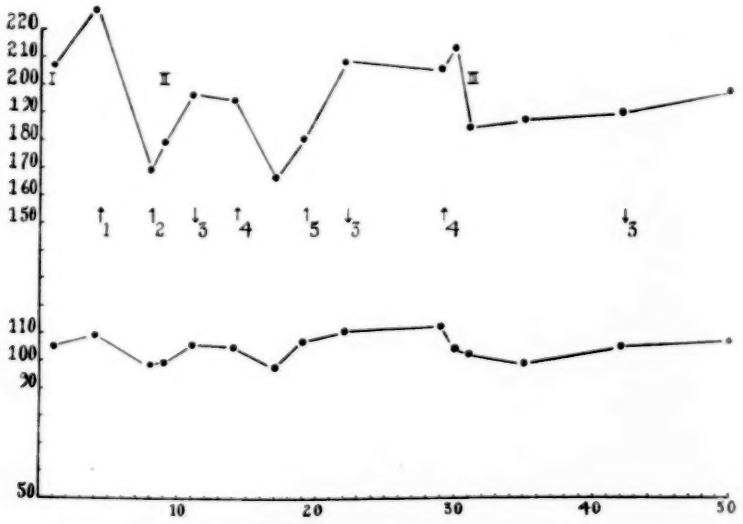


Fig. 2.

Fig. 2.—Curve of Case 12, Table 2, a white man, aged 61. 1, phenobarbital 3 grains (0.19 gm.) three times a day; 2, ¼ grain (0.04 gm.) three times a day; 3, phenobarbital discontinued; 4, 1½ grains (0.09 gm.) three times a day; 5, ¼ grain (0.04 gm.) once a day; I, nonprotein nitrogen, 40 mg. per hundred millimeters of blood and phenolsulphonephthalein, 37 per cent.; II, nonprotein nitrogen, 36.3 mg. and phenolsulphonephthalein, 40 per cent.; III, nonprotein nitrogen, 40.8 mg., and phenolsulphonephthalein, 42 per cent.

treatment, only the blood pressure on the day immediately before treatment and the lowest pressure during treatment and again the highest pressure following treatment are given here. We have thus far found no indication that phenobarbital increases blood pressure before producing its depression as was thought to be the case by Impens.[1]

Charts 1 and 2 are presented to show more clearly the effect of phenobarbital on both systolic and diastolic blood pressures. In Chart 1, a colored woman, aged 68, was treated in the routine manner in the dispensary for several weeks before receiving phenobarbital. Her average blood pressure determined in millimeters of mercury on entrance was 230 systolic and 121 diastolic. This fell to 219 systolic and 115 diastolic after twenty days of routine treatment. Phenobarbital, 1½ grains (0.09 gm.), three times a day was given at 1. Two days later the average blood pressure for the three ten minute periods was 184 systolic and 98 diastolic, and four days later, or six days after beginning treatment, it was 171 systolic and 102 diastolic. Phenobarbital treatment was then withdrawn and the systolic pressure returned to 215 mm. of mercury and the diastolic to 110.

In Chart 2, a white man, aged 61, who had previously submitted to a twelve day course of benzyl benzoate treatment without results,[27] was given phenobarbital. Through some misunderstanding, this patient took 3 grains (0.19 gm.) of phenobarbital three times a day for four days at 1. His average systolic blood pressure for the three readings for the day fell from 227 to 169 mm. of mercury and his diastolic from 109 to 98. At 4, the patient took 1½ grains (0.09 gm.) three times a day with good results, as seen in the chart. Smaller doses were less effective in lowering blood pressure at 2 and 5. In the chart, each 3 indicates a discontinuance of phenobarbital administration.

### HOSPITAL CASES

It may be thought that the fall in blood pressure in the ambulatory cases under phenobarbital treatment was due to the hypnotic action of the drug and consequent quieting of the patient. Such, however, is not the case. Phenobarbital produces the same effect in patients at rest as in those up and about. This mode of therapy was tested in eight hospital cases. The first two cases in Table 3 were cases in Barnes Hospital, while the others were patients at St. Louis City Hospital. The fall in blood pressure in these cases was as marked as in our ambulatory cases.

The results obtained from Patient 1 are plotted in Chart 3. In Chart 3, the patient had been kept in bed for six days before phenobarbital was started at 1. She received 1½ grains (0.09 gm.) of phenobarbital three times a day at 1, at 2 the same quantity twice, and at 3 once a day. At 4 the treatment was discontinued. It will be seen that the average of the six readings of the systolic pressure before treatment and the average of all the readings following it show a fall

27. Gruber and Schakelford (Footnote 25, Fig. 4).

of 36 mm., and that the average diastolic pressure fell 15 mm. of mercury. The maximum systolic fall was 54 mm. and the maximum diastolic fall was 34 mm. of mercury.

### EFFECT OF PHENOBARBITAL ON KIDNEY FUNCTION

Although phenobarbital is eliminated in the urine, most observers agree that it has no detrimental effect on the kidneys. Among these

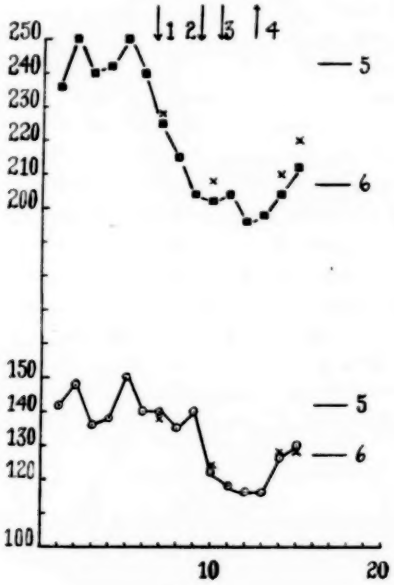


Fig. 3.

Fig. 3.—Curve of Case 2, Table 2, a white woman, aged 39. The top record is the systolic blood pressure, the bottom record diastolic blood pressure. The time in days is plotted on the abscissa and the blood pressure in millimeters of mercury on the ordinate. 1, phenobarbital given, 1½ grains (0.09 gm.) three times a day; 2, phenobarbital, 1½ grains twice a day; 3, phenobarbital, 1½ grains once a day; 4, phenobarbital discontinued; 5, average of all the blood pressure readings after phenobarbital.

are Impens,[1] Kino,[8] Kirk,[12] Weber,[28] Stein [29] and Geisler.[30] Goldstein,[10] Hueber [31] and Phillips [32] report the appearance of albumin in the urine,

28. Weber, Hannes: Therap. Halbmonatsch. **35**:467 (Aug. 1) 1921; Klin. Wchnschr. **1**:998 (May 13) 1922.
29. Stein, J.: Therap. Halbmonatsch. **34**:387 (July 15) 1920.
30. Geisler: München. med. Wchnschr. **59**:922, 1912.
31. Hueber: München. med. Wchnschr. **66**:1090, 1919.
32. Phillips, John: Phenobarbital (Luminal) Poisoning, J. A. M. A. **78**:1199 (April 22) 1922.

and the latter author believes it also capable of producing nephritis. Our observations in the main support the former view, but certain changes in the phenolsulphonephthalein excretion were noted in our patients while under phenobarbital treatment. In most instances shortly after starting treatment, the percentage of phenolsulphonephthalein excretion increased. This is observed in Charts 1 and 2 and in Table 2. We might be inclined to believe this to be due to an increased kidney function as a result of the fall in blood pressure except for the fact that an increase occurred in some cases in which the blood pressure was already fairly low. On the other hand, prolonged administration seems to decrease the rate of elimination of phenolsulphonephthalein (Table 2). This may be explained as being due to increased rate of destruction of the phenol derivatives after the tissues have been exposed to phenobarbital for a long time. After the withdrawal of phenobarbital for a short time the phenolsulphonephthalein excretion appears to be restored to its former level. These results do not attempt to prove anything but are simply suggestive of changes since wide variations from week to week occur, even in normal subjects.

The effect of phenobarbital on the kidney function was studied on two female dogs. These animals weighed 20 kg. each, and were given phenobarbital by mouth. The phenolsulphonephthalein readings were taken before and during administration. The urine was collected by catheterization. One animal received phenobarbital, 1½ grains (0.09 gm.) three times a day for fifteen days, after which time she was given 3 grains (0.19 gm.) three times a day for nine days. The other was started at once on 3 grains (0.19 gm.) three times a day, and was given the drug for nine days. The results were quite uniform. The percentage of phenolsulphonephthalein excreted in Dog 1 before the drug was given was 58 and 54, and during the drug administration 49, 65, 42 and 50 per cent. In Dog 2 the control readings were 44 and 47 per cent., and those while the animal was taking the drug were 48 and 47 per cent. Phenobarbital as far as we could determine has no effect on the kidney function when given in even as large doses as 9 grains (0.6 gm.) per day. The urine showed no casts or albumin. It gave a definite sugar reduction with Benedict's and Fehling's solutions on prolonged boiling. This may be due to the elimination of phenobarbital in combination with glycuronic acid. It seems, therefore, that the results noted in our patients must have been due to other factors than the administration of phenobarbital.

### TOXICITY OF PHENOBARBITAL

Many men who have used phenobarbital in the treatment of epilepsy believe that the use of phenobarbital without discrimination will be

followed by lamentable results. It is not atoxic. Prolonged use in small doses or its use in large doses over a shorter period may be accompanied by a variety of toxic symptoms. This is especially true in hypersusceptible persons. There have appeared in the literature over 100 cases of poisoning with four fatalities attributed to its use. Any or all of the following symptoms may be noted after prolonged use of fairly large doses: asthenia, ataxia, vertigo with a tendency to fall backward; either dilatation or constriction of the pupils, conjunctivitis, nystagmus, diplopia, blindness; sleepiness to complete loss of consciousness, headache, mental apathy, hallucinations (auditory and visual), delusions and mental defects (tendency to cry), also mental symptoms simulating alcoholic intoxication (the patient becoming loquacious, excited, exalted and manifesting a flippant behavior), slow slurring speech to total loss, inflammation of pharynx, swollen reddened tongue, with denuded epithelial areas, which takes on a raw, beefy appearance, red gum line, appearance of thin walled blisters filled with blood fluid on the lips, which later ulcerate; anorexia, nausea, vomiting, diarrhea with mucous stools containing blood, atony of the intestine; atony of the urinary bladder, either anesthesia of the skin or pruritis, cutaneous rash resembling measles or scarlet fever, with small petechiae; increased body temperature; Cheyne-Stokes respiration; either bradycardia or tachycardia, and fall in blood pressure.

Although a host of changes are seen in toxic cases, yet the drug is relatively nontoxic when given properly. The range between the therapeutic and the toxic dose is large. Patients have taken as much as 3 gm. of phenobarbital in a single dose without causing death,[33] and the four deaths attributed to phenobarbital were probably not wholly due to the drug but due to other causes. The most common symptoms are sleepiness, asthenia, vertigo, ataxia and pruritis. In the literature the cutaneous rashes were reported thirty-four times in 109 toxic cases by Gregor,[4] Galla,[18] Grinker,[19] Weber,[28] Hueber,[31] Phillips,[32] Patschke,[34] Emanuel,[35] Greenwald,[36] Haug,[37] Blichert,[38] Eder,[39] Herrmann,[40] Ashmore,[41] von Klebelsberg,[42] Zimmermann,[43] Strauss,[44] Chargin [45] and

33. Nicolai: Klin. Wchnschr. **2**:1891, 1923.
34. Patschke: Neurol. Centralbl. **31**:899, 1912.
35. Emanuel: Neurol. Centralbl. **31**:563, 1912.
36. Greenwald, J. G.: New York M. J. **116**:356 (Sept. 20) 1922.
37. Haug: München. med. Wchnschr. **66**:1494, 1919.
38. Blichert: Ugesk. f. Laeger, Kjøbenh. **75**:1149, 1913.
39. Eder: Therap. d. Gegenw., Berlin, **53**:258, 1912.
40. Herrmann, R.: Klin. Wchnschr. **2**:212 (Jan. 29) 1923.
41. Ashmore, B. L.: Boston M. & S. J. **187**:950 (Dec 28) 1922.
42. Von Klebelsberg: Psychol. Neurol. Wchnschr., 1912, p. 415.
43. Zimmermann: Therap. Halbmonatsch. **34**:79, 1920.
44. Strauss: Therap. Halbmonatsch. **31**:338, 1917.
45. Chargin, L.: Transactions New York Academy of Medicine, Arch. Dermat. & Syph. **6**:222 (Aug.) 1922.

others. This rash is usually described as resembling measles or scarlet fever. Rosen [46] enumerates four types of phenobarbital eruptions of the mucous membranes: the pemphigoid, morbilliform, scarlatiniform and erythema multiforme. Chargin [45] believes ethylphenylbarbituric acid eruption to be due to the amido or the phenyl radical which presumably breaks up certain of the proteins in the system causing them to act much like foreign proteins. The fact that phenobarbital produces cutaneous vasodilatation [3] in this area may be an important factor in the production of the rash. The drug may produce here a capillary paralysis as well as a relaxation of the arterioles and venules.

The four possible fatal cases reported in the literature as a result of phenobarbital administration are those by Schaefer,[47] Hueber,[31] Rosenberger [48] and Ashmore.[41] Schaefer administered to a male patient with chronic bronchitis and marked arteriosclerosis 0.4 gm. the first night and 0.5 gm. subcutaneously the second evening. Five days later, the patient developed hypostatic pneumonia and heart failure from which he died. The case reported by Hueber was that of a man, aged 40. He was given about 0.5 gm. of sodium phenobarbital a day. Thirty days later, he developed a rash, anuria, fever, cough, vomiting and active tuberculosis. His death was due to the development of active fulminant miliary tuberculosis. Hueber doubts very much if death was due to the drug but believes that it may have been a contributing factor. Rosenberger's case was that of a woman, aged 31, who took forty 1 grain tablets of phenobarbital and 10 c.c. of tincture of opium for suicidal purposes. She died two days later. Ashmore reports a case of a negro man, aged 36, who had taken phenobarbital for forty-one days, after which an eruption appeared on the face and body but disappeared when phenobarbital was withdrawn. Without further treatment, fourteen days following the first appearance the eruptions reappeared. This was accompanied by edema of the eyelids, conjunctivitis, and reddened membranes of the mouth and throat. The tonsils and tongue were swollen, and he presented symptoms of acute bronchitis. The temperature did not go above 102.6 F., the pulse rate above 124, or respiration rate above 30. The spots that were separated became more noticeable and confluent and took on the form of a desquamating eczema, with a tendency to ulcerations with pustule formation. The patient died twenty-seven days after the first appearance of the symptoms.

In our cases (Table 2) we noted no rashes. Some of the patients complained of intoxication with a tendency to fall backward, sleepiness,

46. Rosen: Transactions New York Academy of Medicine, Arch. Dermat & Syph. **6**:223 (Aug.) 1922.
47. Schaefer: Berl. klin. Wchnschr. **49**:1038, 1912.
48. Rosenberger: Med. Klin. **15**:1150, 1919.

vertigo, pruritis, a pricking sensation of the skin and asthenia. None of these symptoms were sufficiently severe to require reduction of the dose to less than 1½ grains (0.09 gm.) twice a day.

## COMMENT

Phenobarbital (luminal) caused a fall in arterial blood pressure in the treatment of arterial hypertension in about 85 per cent. of our cases. On prolonged use it became less and less effective. There were observed no serious side actions. It is, as far as we know, nonhabit forming, according to Dercum,[11] Kirk,[12] Raecke,[13] Darling,[17] Grinker,[19] Hauptmann,[24] Brühl [49] and Wender and Sampson.[50] In our own cases, it was withdrawn without the slightest psychic effect on the patients. After withdrawal we did not note in any instance a marked increase in blood pressure above the control level and in many cases it remained low. It seems to have less effect on the increased blood pressure in cases of acute nephritis with cardiac decompensation than on the chronic nephritic cases and on hypertension observed in arteriosclerotic ones. There appears to be some cumulative action, and we believe that the drug should be discontinued for a short time and the patient treated either in a routine manner or with sodium nitrite during these intervals. Prolonged use appears to decrease phenolsulphonephthalein elimination in the urine after an interval of increased elimination. The mode of action has not been determined.

Most of our patients said they felt improved, were temporarily at least stronger and had less headache until the toxic effect was reached. The authors warn against a too sanguine view of phenobarbital in the treatment of hypertension. It is at best not a cure, although the improvement in many instances appears most gratifying. We have cited absolute failure in four cases.

## SUMMARY

1. Phenobarbital decreased the arterial blood pressure in 85 per cent. of our cases of hypertension in which it was used.

2. It appears to become less and less effective in most instances on prolonged administration.

3. It has the same effect on both ambulatory and hospital patients.

4. In moderate doses it has probably no harmful effect on the kidney tissues and on the phenolsulphonephthalein excretion. Immediately with the fall in blood pressure the phenolsulphonephthalein excretion is increased but later, in some instances, its elimination is

49. Brühl, F.: München. med. Wchnschr. **67**:990 (Aug. 20) 1920.
50. Wender, L., and Sampson, D. G.: New York M. J. **116**:336 (Sept. 20) 1922.

diminished. The elimination again returns to its original level after withdrawal of the drug.

5. It produces marked toxic symptoms in large doses and therefore should not be prescribed indiscriminately.

# BASAL METABOLISM AS AFFECTED BY ATMOSPHERIC CONDITIONS

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The constancy in the basal metabolism of human beings has been emphasized recently by Lusk and DuBois,[1] who compiled data showing that a man between 30 and 40 years of age may show a basal metabolism during eleven years within a variation of ± 7.6 per cent. Zuntz [2] likewise recorded his basal metabolism at intervals over a period of twenty-nine years with little variation. Other physiologic measurements such as body temperature, pulse rate and, in lesser degree, blood pressure under favorable conditions show a similar uniformity.

A high environmental temperature is an important factor in altering this uniformity in physiologic reactions, and often in certain industries marked deviations from the normal occur in workmen who are daily exposed to abnormally high temperatures.

While the human body has the ability to adapt itself to a fairly wide range in temperatures, its capacity for adjustment is limited. It has been stated in the literature that water drunk freely during exposure to high air temperature prevents disaster in periods of thermal stress and may even prevent a rise in body temperature, but the work [3] carried on at the Pittsburgh Experiment Station of the Bureau of Mines jointly with the Research Laboratory of the American Society of Heating and Ventilating Engineers clearly demonstrates that water, even when taken in large quantities, had little or no influence in preventing a rise in body temperature in human beings.

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1. Lusk, Graham; and DuBois, E. F.: On the Constancy of the Basal Metabolism, J. Physiol. **59**:213 (Oct.) 1924.

2. Zuntz, N., and Loewry, A.: Berl. klin. Wchnschr. **54**:825, 1916; Biochem. Ztschr. **90**:244, 1918.

3. McConnell, W. J., and Houghten, F. C.: Some Physiological Reactions to High Temperatures and Humidities, J. Am. Soc. Heat. & Vent. Eng. **29**, No. 2, March, 1923. McConnell, W. J.; Houghten, F. C., and Yagloglou, C. P.: Air Motion, High Temperatures and Various Humidities: Reactions on Human Beings, J. Am. Soc. Heat. & Vent. Eng. **30**, No. 3, March, 1924.

While there is considerable material available for the study of changes in body temperature, pulse frequency and blood pressure, little work has been done on human beings showing the relation between the metabolic rate and external temperature conditions.

The difficulty in establishing this relation probably has been due to the fact that in high temperatures the wet bulb temperature of the air becomes more important than the dry bulb temperature in influencing the human body. In addition, air movement, if any, constitutes an equally important factor and in many instances the most powerful of the three. The difficulty in evaluating the relative importance to be attached to these three measurements has only been recently obviated through the development of the effective temperature index, which combines the three physical air factors into a single index.

On this index depends the comfort or discomfort of human beings, as far as atmospheric heat is concerned, and because of the fact that it also determines the physiologic effects of heat on the human body it has been called "effective temperature index."

## EFFECTIVE TEMPERATURE

To form a clear conception of what effective temperature is, it will be desirable to take up briefly the development of this index. In Figure 1 the horizontal scale represents the dry bulb and the vertical scale the wet bulb temperature of the air. When the air is saturated with moisture the dry and the wet bulb temperatures have the same numerical value. Therefore, the diagonal line *ab* represents the saturation line. Suppose now that there are two chambers in which the temperature and humidity can be controlled independently of each other, and that a saturated condition of 70 degrees is produced and maintained in one of the chambers. This condition is represented in Figure 1 by *c*. If the wet bulb temperature in the second chamber is kept lower than that in the first chamber, and the feelings of warmth of the two are compared by human subjects, it will be found that its dry bulb temperature must be increased for the warmth and comfort of the two conditions to be the same. This also follows from a consideration of the fact that the human body loses heat first by radiation and convection, which depends on the dry bulb temperature of the air and of the surrounding walls and objects, and second by evaporation of moisture from its surface, the latter depending on the wet bulb depression (arithmetical difference between the dry and wet bulb temperature of the air). Thus an air condition with a dry bulb temperature of 72.5 degrees and a wet bulb temperature of 68 degrees, represented by *d*, will be found equally warm and equally comfortable as the saturated condition of 70 degrees when the comparison is made by individuals stripped to the waist and in still air.

If the wet bulb temperature in the second room is further reduced, keeping the saturated condition in the first room constant, a still higher dry bulb temperature will be required for the same degree of comfort. Thus, conditions represented by *c* and *f* will be found to be equally warm as the original condition at *c*. A line drawn through these points gives all other equivalent conditions of the same degree of warmth and comfort.

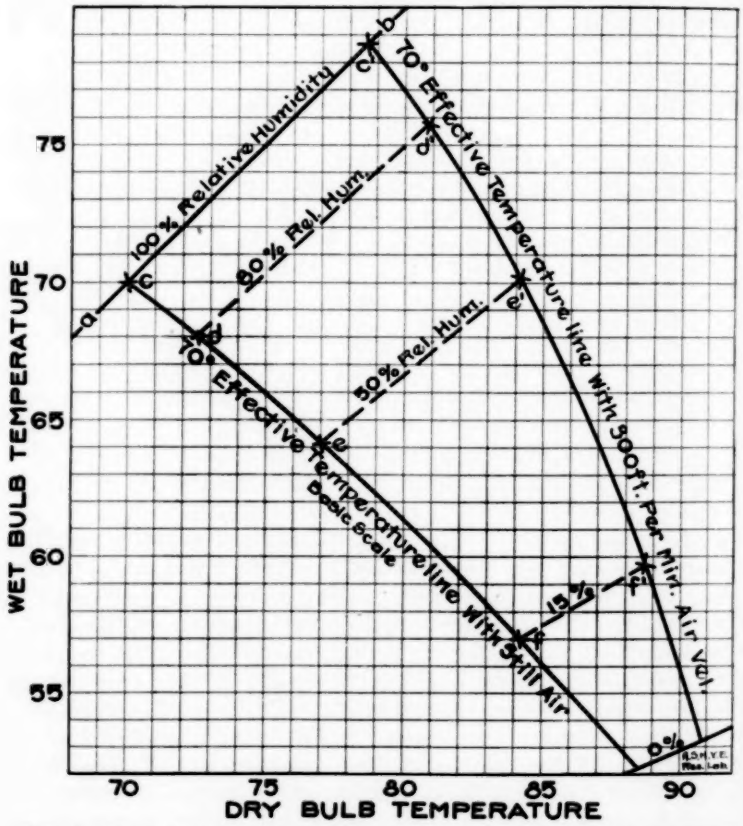


Fig. 1.—Equivalent conditions of temperature, humidity and air movement of 300 feet per minute, corresponding to an effective temperature of 70 degrees F.

In similar manner other lines can be determined with lower and higher saturated temperature conditions in the first room, giving thus a series of lines, one for each degree of saturation temperature. The numerical value of these lines is fixed by the saturation temperature of their equivalent condition; for instance, line *cf* is the 70 degrees effective

temperature line with still air, while the next higher is the 71 degrees, and the next lower is the 69 degrees effective temperature line.

In the foregoing procedure all conditions of the same effective temperature index were called "equivalent conditions of temperature and humidity" only, so far as they were determined with still air in both chambers. If now in one of the chambers the conditions represented by *c, d, e* and *f* are produced successively with still air, and a certain uniform velocity is set up in the second chamber, it will be found that with the same relative humidity in both chambers the dry bulb temperature in the velocity room must be increased to the values represented by *c'*, *d'*, *e'* and *f'*, to counterbalance the cooling effect of wind on the human body. Line c'f' is the 70 degrees effective temperature line with a velocity of 300 feet per minute. In other words, all conditions on line *c'f'* with a velocity of 300 feet per minute are equally comfortable among themselves and also equally comfortable to all conditions on line *cf* with still air.

The complete results of the investigation on effective temperature covering a range of from 28 to 170 degrees F. dry bulb and from 25 to 115 degrees F. wet bulb temperature, for human beings at rest and both stripped to the waist and normally clothed, have appeared in several issues of the Journal of the American Society of Heating and Ventilating Engineers [4] and in other domestic and foreign publications.

With the development of the effective temperature index the effect of heat on body metabolism can be easily studied, since the factors entering into the problem can be reduced to two variables, one of which (rate of metabolism) is the independent variable.

## CORRELATION OF METABOLIC RATE AND EFFECTIVE TEMPERATURE

A previous analysis [5] of the results of several investigators, including those obtained in the psychrometric chambers of this society's Research Laboratory, disclosed that such correlation between the metabolic rate and effective temperature does exist. However, the correlation for the higher temperatures is based on the results obtained

4. Houghten, F. C., and Yagloglou, C. P.: Determining Lines of Equal Comfort, J. Am. Soc. Heat. & Vent. Eng. **29**:165-176 (March) 1923; Determination of the Comfort Zone and Further Verification of Effective Temperature Within this Zone, ibid. **29**:515-536, 1923; Cooling Effect on Human Beings Produced by Various Air Velocities, ibid. **30**:169-184 (Feb.) 1924. Yagloglou, C. P., and Miller, W. E.: Effective Temperature Applied to Industrial Ventilation Problems, ibid. **30**:515-539 (July) 1924; Equivalent Conditions of Temperature Humidity and Air Movement Determined by Subjects Normally Clothed: Effective Temperature with Clothing, ibid. **31**:59-70 (Jan.) 1925.

5. Yagloglou, C. P.: The Heat Given Up by the Human Body and Its Effect on Heating and Ventilating Problems, J. Am. Soc. Heat. & Vent. Eng. **30**, No. 4, August, 1924.

on a single individual, and therefore it does not represent an average of what is expected at high temperatures.

In subsequent exhaustive experiments conducted in the psychrometric chambers of the Research Laboratory, seven subjects took part in the tests. To disentangle the influence of routine factors, such as food and muscular activity, on the rate of metabolism, the subjects refrained from eating for a period of eight hours prior to every experiment and abstained from any undue physical exertion.

During the first two hours of the experiment each subject rested quietly on a cot provided for the purpose in a primary room. A sample of expired air was then taken from each subject at the expiration of the two hours, and the subject was carried on the stretcher into the

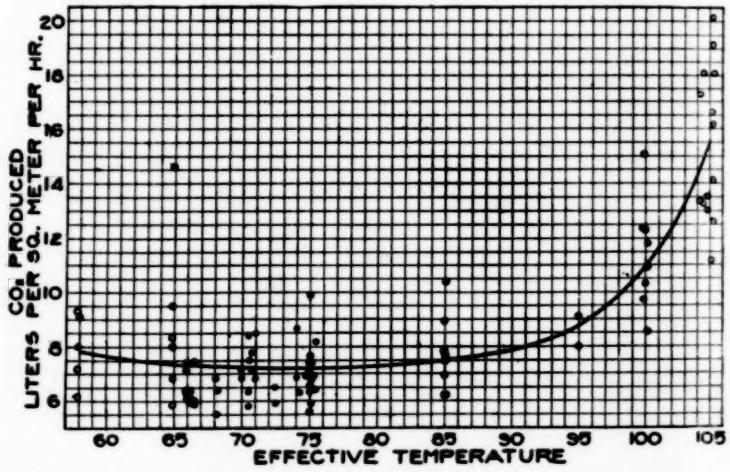


Fig. 2.—Relation between effective temperature and liters of carbon dioxid expired by each subject per square meter of body surface per hour.

conditioned test chamber where he continued to rest in the same position. He remained in the chamber over a period varying with his ability to endure the condition. During the exposure in the chamber samples of expired air were again taken. All these experiments were conducted in still air, which was renewed at an adequate rate.

The average normal measurements for the subjects employed in the experiments are shown in Table 1. The body surface was determined from these by means of the DuBois standard chart. The subjects wore light weight union underwear, work pants and shirts, socks and shoes.

The samples of expired air were collected by means of a graduated gasometer constructed by the Bureau of Mines and placed in a room

adjoining the test chamber. Rubber tubing (1¼ inch) connected the gasometer with the mouthpiece, the valves [6] of which were likewise constructed by the Bureau of Mines. To become accustomed to the apparatus, the subjects breathed through the gasometer for several minutes before samples were taken. This permitted the stagnant air in the system to be forced out. Each sample collected consisted of approximately 60 liters of expired air. All volumes were reduced to 0 C. temperature and dry and 760 mm. of mercury barometric pressure. The ventilation rate or volume of air expired per minute was obtained by dividing the total volume by the time in minutes. From each sample collected an average sample was analyzed on a large Haldane apparatus [7] for carbon dioxid and oxygen from which the heat developed within the body under the various temperature conditions was computed, using Zuntz's table of calorific equivalents of 1 liter of oxygen.

The data and results of the present series of experiments are presented in Table 2. Temperature conditions of the primary room are given at the left of Column 3, and those of the test chamber at the right

TABLE 1.—*Statistics of Subjects of Experiments*

| Subjects | Weight, Kg. | Height, Cm. | Body Surface, Sq. Meters |
|---|---|---|---|
| 1 | 61.6 | 163.0 | 1.66 |
| 2 | 64.5 | 183.1 | 1.84 |
| 3 | 69.5 | 191.0 | 1.97 |
| 4 | 72.0 | 171.3 | 1.84 |
| 5 | 59.2 | 167.0 | 1.68 |
| 6 | 59.4 | 172.8 | 1.72 |
| 7 | 71.1 | 174.7 | 1.82 |

of the same column. The length of exposure before taking samples is shown in Column 4. The carbon dioxid produced and the oxygen absorbed in liters per hour at 0 C. temperature and 760 mm. of mercury barometric pressure are shown in Columns 5 and 6, respectively.

The computed ratio of the former to the latter, or respiratory quotient, is given in Column 7. The total number of calories developed per hour is given in Column 8, from which is calculated the heat produced within the body per square meter of body surface per hour, given in Column 9. Columns 10 and 11 give the average physiologic reactions recorded during the period during which the samples were taken.

It will be observed that both the carbon dioxid output and the oxygen consumed increase with exposure to either high or low temperatures. The range of temperature employed in the experiments

6. Fulton, W. B.: An Improved Air Valve for Apparatus Used in Basal Metabolism Work, Arch. Int. Med. **33**:497-499 (April) 1924.

7. Burrell, G. A., and Seibert, F. M.: The Sampling and Examination of Mine Gases and Natural Gas, Bull. 42, Bureau of Mines, revised by G. W. Jones, 1924, to be published.

TABLE 2.—*Data and Results of Experiments*

| Test No. and Date | Subjects | Test Room Conditions: Primary Dry Bulb | Primary Wet Bulb | Primary Effective Temp. | Secondary Dry Bulb | Secondary Wet Bulb | Secondary Effective Temp. | Exposure Before Taking Sample: Primary Room Hours | Primary Room Minutes | Secondary Room Hours | Secondary Room Minutes | Carbon Dioxid Produced Liters per Hour | Oxygen Consumed Liters per Hour | Respiratory Quotient | Total Calories per Hour | Calories per Sq. M. of Body Surface per Hour | Rectal Temperature, F. | Pulse Rate, Beats per Minute |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 A. S. | 1 | 75.0 | 66.8 | 70.5 | ..... | ..... | ..... | 2 | 00 | ... | .. | 9.60 | 10.92 | 0.879 | 53.5 | 32.6 | 98.0 | 72 |
| 6/4/23 | 1 | .... | .... | .... | 105.6 | 104.2 | 104.3 | ... | .. | 2 | 00 | 22.14 | 22.50 | 0.984 | 113.1 | 69.2 | 102.1 | 158 |
| | 2 | 75 0 | 66.8 | 70.5 | ..... | ..... | ..... | 2 | 30 | ... | .. | 15.36 | 16.44 | 0.934 | 81.6 | 44.3 | 98.4 | 64 |
| | 2 | .... | .... | .... | 105.6 | 104.2 | 104.3 | ... | .. | 0 | 56 | 31.74 | 31.44 | 1.009 | 158.9 | 87.7 | 102.5 | 158 |
| 38 A. S. | 1 | 76.4 | 64.2 | 70.0 | ..... | ..... | ..... | 2 | 00 | ... | .. | 11.76 | 13.38 | 0.878 | 65.6 | 39.5 | 98.0 | 68 |
| 6/8/23 | 1 | .... | .... | .... | 100.0 | 100.0 | 100.0 | ... | .. | 1 | 37 | 16.86 | 15.84 | 1.063 | 81.1 | 49.4 | 101.7 | 132 |
| | 2 | 76.4 | 64.2 | 70.0 | ..... | ..... | ..... | 2 | 25 | ... | .. | 12.48 | 13.44 | 0.929 | 66.7 | 36.8 | 98.2 | 60 |
| | 2 | .... | .... | .... | 99.9 | 99.9 | 99.9 | ... | .. | 1 | 14 | 22.62 | 22.50 | 1.005 | 113.7 | 62.7 | 101.8 | 150 |
| 39 A. S. | 1 | 77 0 | 69.0 | 72.5 | ..... | ..... | ..... | 2 | 00 | ... | .. | 9.66 | 11.10 | 0.870 | 54.3 | 33.2 | 98.0 | 80 |
| 6/11/23 | 1 | .... | .... | .... | 95.0 | 95.0 | 95.0 | ... | .. | 1 | 54 | 13.20 | 13.74 | 0.961 | 68.6 | 41.9 | 99.3 | 96 |
| | 2 | 77.0 | 69.0 | 72.5 | ..... | ..... | ..... | 2 | 30 | ... | .. | 11.88 | 13.08 | 0.908 | 64.6 | 35.6 | 99.0 | 76 |
| | 2 | .... | .... | .... | 95.0 | 95.0 | 95.0 | ... | .. | 2 | 1 | 16.62 | 18.90 | 0.879 | 92.6 | 51.2 | 100.1 | 96 |
| 40 A. S. | 1 | 76.0 | 67.0 | 71.0 | ..... | ..... | ..... | 1 | 30 | ... | .. | 11.22 | 12.60 | 0.898 | 61.9 | 37.4 | 98.4 | 72 |
| 6/27/23 | 1 | .... | .... | .... | 104.6 | 104.6 | 104.6 | ... | .. | 1 | 2 | 29.82 | 26.34 | 1.130 | 137.5 | 83.8 | 102.0 | 140 |
| | 2 | 76.0 | 67.0 | 71.0 | ..... | ..... | ..... | 1 | 50 | ... | .. | 15.66 | 16.32 | 0.960 | 81.5 | 43.3 | 98.0 | 70 |
| | 2 | .... | .... | .... | 104.6 | 104.6 | 104.6 | ... | .. | 0 | 54 | 24.48 | 25.44 | 0.963 | 127.8 | 69.5 | 101.8 | 145 |
| 41 A. S. | 1 | 79.5 | 63.0 | 70.6 | ..... | ..... | ..... | 1 | 30 | ... | .. | 10.32 | 10.56 | 0.978 | 52.9 | 32.1 | 98.0 | 74 |
| 6/29/23 | 1 | .... | .... | .... | 105.3 | 105.3 | 105.3 | ... | .. | 1 | 00 | 23.16 | 22.26 | 1.040 | 113.5 | 68.7 | 100.8 | 114 |
| | 1 | .... | .... | .... | 105.3 | 105.3 | 105.3 | ... | .. | 1 | 30 | 27.42 | 25.20 | 1.087 | 129.3 | 79.3 | 101.9 | 136 |
| | 2 | 79.5 | 63.0 | 70.6 | ..... | ..... | ..... | 1 | 50 | ... | .. | 13.74 | 14.28 | 0.962 | 71.4 | 39.4 | 99.0 | 70 |
| | 2 | .... | .... | .... | 105.3 | 105.3 | 105.3 | ... | .. | 0 | 54 | 23.22 | 22.50 | 1.032 | 114.4 | 63.2 | 100.6 | 128 |
| 42 A. S. | 1 | 77.2 | 65.3 | 70.7 | ..... | ..... | ..... | 1 | 30 | ... | .. | 11.94 | 12.36 | 0.966 | 61.9 | 37.7 | 97.8 | 80 |
| 7/2/23 | 1 | .... | .... | .... | 105.1 | 105.1 | 105.1 | ... | .. | 0 | 58 | 18.48 | 16.80 | 1.100 | 86.8 | 52.9 | 100.8 | 120 |
| | 1 | .... | .... | .... | 105.1 | 105.1 | 105.1 | ... | .. | 1 | 18 | 33.36 | 27.84 | 1.200 | 147.1 | 88.6 | 102.3 | 136 |
| | 2 | 77.2 | 65.3 | 70.7 | ..... | ..... | ..... | 1 | 50 | ... | .. | 14.40 | 15.90 | 0.906 | 78.4 | 43.3 | 98.0 | 82 |
| | 2 | .... | .... | .... | 105.1 | 105.1 | 105.1 | ... | .. | 0 | 53 | 29.88 | 26.88 | 1.112 | 139.3 | 75.6 | 101.6 | 144 |
| 43 A. S. | 3 | 79.7 | 72.8 | 75.5 | ..... | ..... | ..... | 1 | 30 | ... | .. | 12.48 | 14.04 | 0.889 | 69.0 | 35.2 | 98.0 | 64 |
| 7/6/23 | 3 | .... | .... | .... | 140.0 | 98.2 | 100.1 | ... | .. | 1 | 21 | 16.68 | 16.02 | 1.041 | 81.6 | 41.7 | 101.1 | 105 |
| | 3 | .... | .... | .... | 140.0 | 98.2 | 100.1 | ... | .. | 2 | 10 | 21.36 | 19.20 | 1.112 | 99.4 | 50.7 | 102.3 | 112 |
| | 2 | 79 7 | 72.8 | 75.5 | ..... | ..... | ..... | 1 | 50 | ... | .. | 15.12 | 15.90 | 0.951 | 79.3 | 43.2 | 98.0 | 72 |
| | 2 | .... | .... | .... | 140.0 | 98.2 | 100.1 | ... | .. | 1 | 21 | 21.78 | 21.48 | 1.013 | 108.6 | 59.1 | 101.1 | 114 |
| 44 A. S. | 4 | 80.7 | 69.8 | 74.3 | ..... | ..... | ..... | 2 | 00 | ... | .. | 11.38 | 12.30 | 0.942 | 61.2 | 33.3 | 99.0 | 70 |
| 7/10/23 | 4 | .... | .... | .... | 104.8 | 104.8 | 104.8 | ... | .. | 1 | 00 | 23.70 | 19.02 | 1.246 | 101.6 | 55.2 | 101.3 | 172 |
| | 4 | .... | .... | .... | 104.8 | 104.8 | 104.8 | ... | .. | 1 | 15 | 24.78 | 17.94 | 1.381 | 98.7 | 53.7 | 102.2 | 186 |
| 46 A. S. | 2 | 81.8 | 70.8 | 75.1 | ..... | ..... | ..... | 2 | 00 | ... | .. | 13.56 | 13.68 | 0.992 | 68.9 | 38.1 | 98.6 | 66 |
| 7/13/23 | 2 | .... | .... | .... | 105.3 | 105.3 | 105.3 | ... | .. | 0 | 50 | 33.18 | 26.10 | 1.269 | 140.3 | 76.2 | 101.7 | 134 |
| | 2 | .... | .... | .... | 105.3 | 105.3 | 105.3 | ... | .. | 1 | 10 | 35.22 | 21.84 | 1.612 | 126.3 | 69.8 | 102.4 | 140 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 A. S. | 1 | 82.1 | 68.2 | 74.0 | ..... | ..... | ..... | 1 | 35 | ... | .. | 11.22 | 12.12 | 0.925 | 60.1 | 36.5 | 98.2 | 75 |
| 7/20/23 | 1 | .... | .... | .... | 100.0 | 99.9 | 99.9 | ... | .. | 0 | 56 | 16.02 | 15.30 | 1.047 | 78.0 | 47.6 | 100.3 | 104 |
| | 2 | 82.1 | 68.2 | 74.0 | ..... | ..... | ..... | 1 | 55 | ... | .. | 15.90 | 17.28 | 0.920 | 85.5 | 47.3 | 98.4 | 60 |
| | 2 | .... | .... | .... | 100.0 | 99.9 | 99.9 | ... | .. | 0 | 40 | 22.74 | 21.34 | 1.071 | 108.0 | 59.7 | 99.7 | 110 |
| | 2 | .... | .... | .... | 100.0 | 99.9 | 99.9 | ... | .. | 1 | 35 | 27.66 | 28.80 | 0.960 | 145.9 | 79.5 | 102.1 | 160 |
| 50 A. S. | 1 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 1 | 10 | 9.60 | 10.32 | 0.930 | 51.2 | 31.3 | 97.9 | 58 |
| 7/23/23 | 1 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 3 | 16 | 13.14 | 13.44 | 0.977 | 67.4 | 41.2 | 96.8 | 56 |
| | 5 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 0 | 47 | 13.92 | 11.82 | 1.178 | 61.1 | 36.5 | 99.2 | 68 |
| | 5 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 3 | 46 | 24.48 | 15.84 | 1.549 | 90.3 | 53.4 | 97.6 | 62 |
| | 6 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 0 | 18 | 11.52 | 12.00 | 0.960 | 60.0 | 35.3 | 98.0 | 70 |
| | 6 | .... | .... | .... | 65.3 | 64.2 | 64.9 | ... | .. | 3 | 14 | 16.08 | 13.98 | 1.150 | 73.1 | 43.3 | 97.3 | 68 |
| 51 A. S. | 1 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 1 | 31 | 9.66 | 9.30 | 1.039 | 47.4 | 29.2 | 98.2 | 64 |
| 7/24/23 | 1 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 4 | 36 | 10.38 | 10.08 | 1.029 | 51.2 | 31.2 | 98.0 | 60 |
| | 3 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 1 | 55 | 10.98 | 11.16 | 0.985 | 56.1 | 28.7 | 97.9 | 64 |
| | 3 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 5 | 00 | 13.50 | 11.70 | 1.152 | 61.8 | 31.3 | 97.6 | 64 |
| | 6 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 2 | 4 | 11.70 | 11.76 | 0.995 | 59.3 | 35.0 | 98.2 | 63 |
| | 6 | .... | .... | .... | 75.2 | 74.7 | 75.0 | ... | .. | 5 | 11 | 11.76 | 12.12 | 0.970 | 60.7 | 35.8 | 97.8 | 68 |
| 52 A. S. | 6 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 2 | 14 | 11.22 | 10.62 | 1.067 | 54.4 | 32.0 | 98.1 | 70 |
| 7/25/23 | 6 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 3 | 50 | 16.86 | 11.82 | 1.427 | 65.7 | 38.9 | 97.8 | 64 |
| | 6 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 4 | 57 | 13.08 | 11.34 | 1.153 | 59.4 | 35.1 | 97.8 | 64 |
| | 3 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 1 | 58 | 13.38 | 12.00 | 1.115 | 62.2 | 31.7 | 98.0 | 62 |
| | 3 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 3 | 45 | 14.46 | 14.04 | 1.030 | 71.4 | 36.5 | 98.4 | 64 |
| | 3 | .... | .... | .... | 84.7 | 68.3 | 75.0 | ... | .. | 4 | 43 | 13.98 | 12.30 | 1.138 | 64.1 | 32.9 | 98.4 | 66 |
| 53 A. S. | 3 | ... | .... | .... | 102.3 | 77.8 | 85.0 | ... | .. | 2 | 32 | 12.24 | 12.06 | 1.015 | 61.0 | 31.1 | 98.6 | 70 |
| 7/27/23 | 3 | .... | .... | .... | 102.3 | 77.8 | 85.0 | ... | .. | 5 | 8 | 12.24 | 11.70 | 1.048 | 59.7 | 30.5 | 98.6 | 70 |
| | 6 | .... | .... | .... | 102.3 | 77.8 | 85.0 | ... | .. | 2 | 2 | 12.72 | 11.28 | 1.129 | 58.6 | 34.5 | 98.7 | 68 |
| | 6 | .... | .... | .... | 102.3 | 77.8 | 85.0 | ... | .. | 4 | 52 | 15.12 | 13.38 | 1.130 | 68.0 | 39.7 | 98.5 | 70 |
| 54 A. S. | 3 | .... | .... | .... | 85.0 | 85.0 | 85.0 | ... | .. | 1 | 23 | 13.56 | 11.88 | 1.141 | 62.0 | 31.7 | 98.1 | 66 |
| 7/28/23 | 3 | .... | .... | .... | 85.0 | 85.0 | 85.0 | ... | .. | 4 | 11 | 15.06 | 12.24 | 1.230 | 65.2 | 33.3 | 97.8 | 64 |
| | 6 | .... | .... | .... | 85.0 | 85.0 | 85.0 | ... | .. | 1 | 22 | 17.76 | 12.60 | 1.410 | 69.8 | 40.8 | 98.5 | 72 |
| | 6 | .... | .... | .... | 85.0 | 85.0 | 85.0 | ... | .. | 4 | 6 | 13.20 | 10.62 | 1.243 | 56.7 | 33.6 | 98.2 | 66 |
| 1 E. | 1 | 74.5 | 62.5 | 68.2 | ..... | ..... | ..... | 1 | 30 | ... | .. | 10.56 | 11.76 | 0.897 | 57.9 | 35.3 | 98.2 | 72 |
| 7/10/24 | 1 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 0 | 50 | 10.02 | 11.22 | 0.893 | 55.2 | 33.6 | 97.7 | 66 |
| | 1 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 2 | 21 | 10.50 | 11.64 | 0.902 | 57.4 | 35.0 | 97.5 | 60 |
| | 7 | 74.5 | 62.5 | 68.2 | ..... | ..... | ..... | 1 | 40 | ... | .. | 10.14 | 12.12 | 0.837 | 58.8 | 32.0 | 98.9 | 62 |
| | 7 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 1 | 26 | 11.28 | 13.26 | 0.851 | 64.5 | 35.1 | 98.2 | 58 |
| | 7 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 2 | 48 | 11.76 | 13.86 | 0.848 | 67.3 | 36.6 | 98.0 | 57 |
| | 6 | 74.5 | 62.5 | 68.2 | ..... | ..... | ..... | 1 | 50 | ... | .. | 11.58 | 13.44 | 0.862 | 65.6 | 38.7 | 98.4 | 78 |
| | 6 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 1 | 49 | 12.24 | 13.86 | 0.883 | 68.0 | 40.3 | 98.4 | 70 |
| | 6 | .... | .... | .... | 67.6 | 64.3 | 66.0 | ... | .. | 3 | 7 | 12.54 | 14.46 | 0.867 | 70.7 | 41.8 | 98.2 | 69 |
| 2 E. | 1 | 73.7 | 59.2 | 66.5 | ..... | ..... | ..... | 1 | 10 | ... | .. | 9.72 | 10.74 | 0.905 | 53.0 | 32.3 | 98.0 | 72 |
| 7/11/24 | 1 | .... | .... | .... | 59.4 | 55.7 | 57.9 | ... | .. | 1 | 3 | 11.88 | 13.50 | 0.880 | 66.2 | 40.3 | 98.0 | 56 |
| | 7 | 73.7 | 59.2 | 66.5 | ..... | ..... | ..... | 1 | 40 | ... | .. | 10.98 | 12.66 | 0.867 | 61.8 | 33.6 | 98.4 | 59 |
| | 7 | .... | .... | .... | 59.4 | 55.7 | 57.9 | ... | .. | 1 | 31 | 11.34 | 12.12 | 0.935 | 60.2 | 32.7 | 98.3 | 52 |
| | 7 | .... | .... | .... | 59.4 | 55.7 | 57.9 | ... | .. | 2 | 57 | 17.28 | 17.10 | 1.012 | 86.7 | 47.2 | 98.4 | 54 |
| | 6 | 73.7 | 59.2 | 66.5 | ..... | ..... | ..... | 1 | 55 | ... | .. | 12.72 | 13.32 | 0.955 | 66.5 | 38.8 | 98.4 | 76 |
| | 6 | .... | .... | .... | 59.4 | 55.7 | 57.9 | ... | .. | 3 | 10 | 13.50 | 14.58 | 0.926 | 72.3 | 42.7 | 97.8 | 68 |
| | 6 | .... | .... | .... | 59.4 | 55.7 | 57.9 | ... | .. | 2 | 52 | 15.48 | 17.04 | 0.908 | 84.1 | 49.6 | 97.7 | 68 |

varied from about 55 to 130 degrees effective temperature, but the table includes results only up to about 105 degrees. For temperatures above 105 degrees effective temperature, the subjects could not endure the condition long enough to obtain a representative sample, which required at least an hour's exposure, and therefore the few results obtained above 105 degrees are not included herein.

### CARBON DIOXID PRODUCED AND OXYGEN CONSUMED

To afford a uniform basis of comparison between different subjects, the carbon dioxid produced and the oxygen consumed are expressed in liters per square meter of body surface per hour. The variations of these quantities with effective temperature are shown in Figures 2 and 3, respectively.

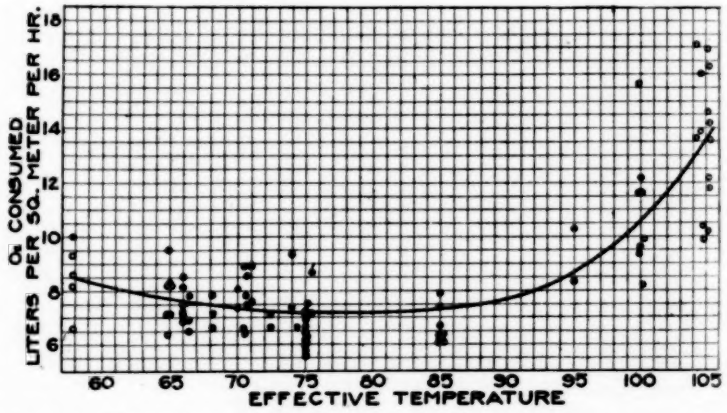


Fig. 3.—Relation between effective temperature and liters of oxygen consumed by each subject per square meter of body surface per hour.

Black circles represent observations made in the primary room, and white or open circles those made in the test chamber. These graphs are very similar and have the same characteristics. A minimum value of 7.2 liters per square meter of body surface per hour is obtained both within a temperature zone of between 70 and 85 degrees effective temperature, where the rate of gaseous exchange is measurably constant. Above and below this zone both quantities increase at an accelerated rate. At the ordinary temperature of 65 degrees effective temperature, the figures show an average of 7.3 liters of carbon dioxid expired and 7.7 liters of oxygen consumed per square meter of body surface per hour. This corresponds to a respiratory quotient of 0.948.

Above 85 degrees effective temperature, the rate of gaseous exchange increases rapidly, and with a still greater rate when the body temperature is exceeded.

It will be observed that in these experiments the respiratory quotient varied from about 0.84 to 1.55. The relation of this ratio to effective temperature, as computed from the average values given in Figures 2 and 3, is shown in Figure 4.

As the effective temperature increases, the respiratory quotient increases also until at about 80 degrees effective temperature it becomes unity. Between 80 degrees and body temperature the variation in the respiratory quotient is rather small; but above body temperature a very sudden increase is apparent, according to the limited results available at these high temperatures. Because of the insufficient number of tests this portion of the curve is shown dotted.

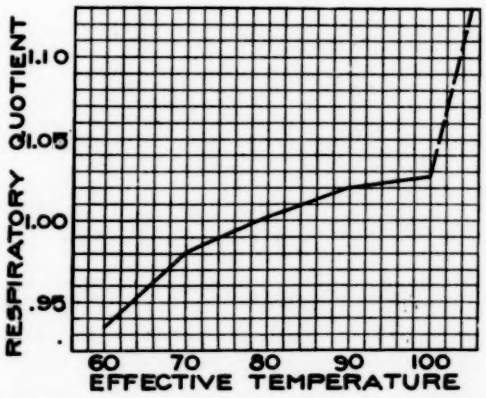


Fig. 4.—Relation between respiratory quotient and effective temperature.

## EFFECT OF HIGH TEMPERATURES ON THE BODY AND RESPIRATORY QUOTIENT

Within the ordinary range of temperature conditions the respiratory quotient, as recorded by various investigators, seldom exceeds unity. The question now arises as to how high temperatures affect the human body so as to raise the respiratory quotient over unity. Theoretical considerations suggest that free oxygen is available in the body through its liberation during the transformation of carbohydrates into fats. A study of the respiratory exchanges of animals which are rapidly laying on a store of fat at the expense of a carbohydrate diet indicates that oxygen is set free. Thus, the marmot eats large quantities of carbohydrate food toward the end of the summer, and rapidly lays on a thick layer of subcutaneous fat to last it during the winter.

Starling [8] points out that a considerable loss of oxygen is incurred in the formation of fat from carbohydrate. He states that if glucose were entirely oxidized in the body the amount of oxygen absorbed would be exactly equal to the amount of carbon dioxid involved. Thus,

$$C_2 H_{12} O_6 + 6 O_2 \; 6 CO_2 + 6 H_2 O$$

In this case the respiratory quotient would be $\frac{6 CO_2}{6 O_2} = 1$

If, however, oxygen is being set free by the conversion of part of the carbohydrate into fat, this oxygen will be available for the oxida-

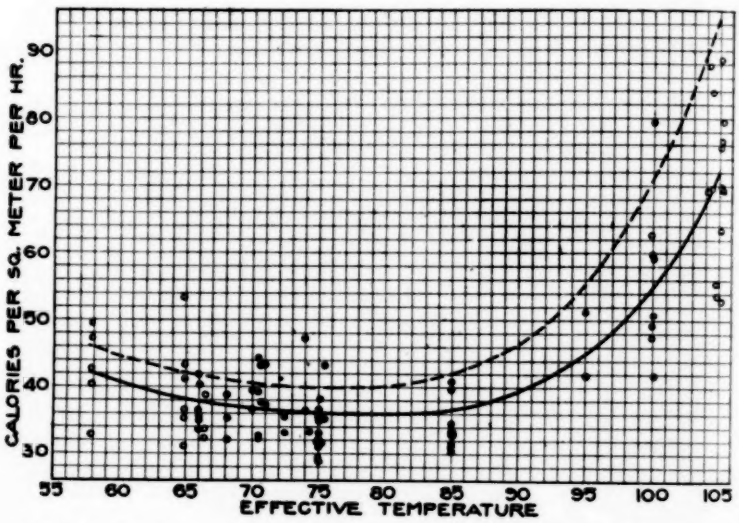


Fig. 5.—Calories produced per square meter of body surface per hour at various effective temperatures.

tion of other portions of the carbohydrates. The animal will not require so much oxygen from external sources for the production of the same amount of carbon dioxid, and therefore the carbon dioxid output of the animal will be greater than its oxygen intake. Pembrey [9] has shown that under this condition the respiratory quotient may be as high as 1.50.

As an alternative hypothesis, it is just as possible that the high respiratory quotient is due to the forced loss of excessive carbon dioxid from the body during exposure. This loss may be either through sweat or through increased breathing, or both.

8. Starling, E. H.: Principles of Human Physiology, Ed. 3, 1920, pp. 826-938.
9. Pembrey: J. Physiol. **27**:407, 1901, cited by Starling (Footnote 8).

The heat produced within the body in calories per square meter of body surface per hour calculated in the manner shown previously is given in Figure 5, plotted against effective temperature. At 65 degrees effective temperature the average subject of the experiments developed 38.2 calories per square meter of body surface per hour. This value checks closely the DuBois' standard for basal metabolism—38.6 calories—but the curve shows that it is by no means the minimum metabolism.

The temperature zone of minimum heat production appears to be between 75 and 83 degrees effective temperature. It will be observed that within this range the lowest value of 36 calories per square meter per hour is reached. This belief is substantiated from results of various

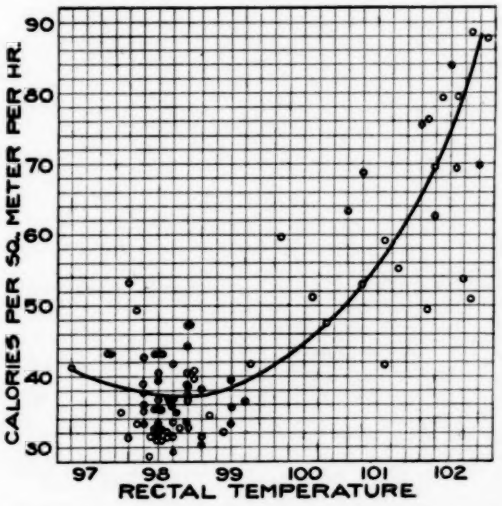


Fig. 6.—Correlation between heat production and rectal temperature.

other investigators who recorded values well below DuBois' standard, depending undoubtedly on the temperature in which the observations were made.

## THERMOSTATIC CONTROL OF THE BODY

Attention is called to the large temperature range of successful operation of the body thermostatic control, within which the heat production and heat loss are accurately balanced. The most economical range is represented by the flat portion of the curve for ordinary atmospheric conditions. Above 85 degrees effective temperature, however, there is apparently a stress on the mechanism. The body makes strenuous efforts to resist rise in its temperature by promoting evaporation of perspiration from its surface, but the limit of adjustment fails

above 90 degrees effective temperature. This is indicated by the rapid increase both of heat production and of body temperature at the higher temperatures. At 105 degrees effective temperature the heat production is twice as great as at the ordinary temperature of 65 degrees.

A tendency for an increase in heat production is also shown below 65 degrees effective temperature, which heat is necessary to keep the body warm in cold surroundings.

### INFLUENCE OF FOOD AND POSTURE ON BODY METABOLISM

To study the influence of food and sitting position on body metabolism it is proposed to introduce here the previous study on metabolism mentioned above.[5] In Figure 5 the dotted line represents the relation

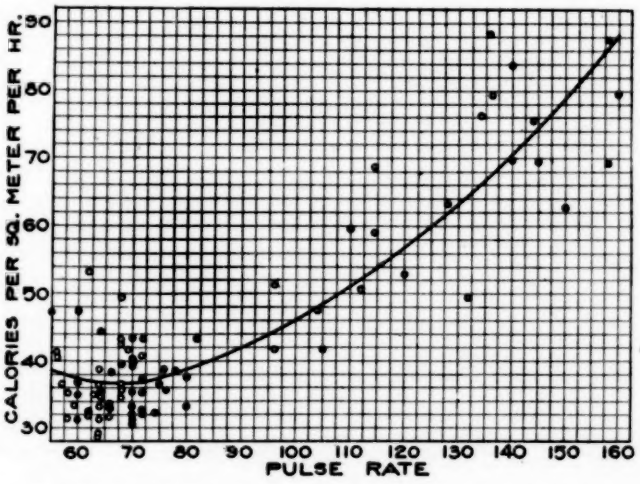


Fig. 7.—Correlation between heat production and pulse rate.

between the metabolic rate and the effective temperature of the exposure when regular meals were partaken and the subjects sat comfortably on chairs. The experimental data from which this relation was drawn are largely based on the results obtained by indirect calorimetry on a subject well trained to the routine of experiments. The respiratory samples were analyzed for carbon dioxid and oxygen on a large Haldane gas apparatus, and the heat production was calculated therefrom after reducing all volumnes to 0 C. and dry and 760 mm. of mercury barometric pressure. Since the experiments under consideration were conducted practically under the same condition of clothing and exposure as those presented in this paper, the difference between the two curves in Figure 5 represents the increase in metabolism due to food and sitting

position. The two curves are practically parallel within the ordinary range of temperature and their difference amounts to about 4 calories per square meter per hour. In other words, the metabolism at the ordinary temperature of 65 degrees increases by 11 per cent. over the basal value when the subjects partake of their regular diet and sit comfortably on chairs.

For the higher temperatures exceeding 80 degrees effective temperature, the increase in metabolism through food and sitting position is not constant but is accelerated as shown by the divergence of the two curves.

It is of interest to note that the temperature zone of minimum metabolism, or the most economical thermal zone of the human body, is included very nearly between the same two temperature limits for both curves. These two limits may possibly vary with the amount of clothing worn, but no great variation is expected, owing to the fact that it was found in another investigation that clothing makes little or no difference in the thermal condition of the human body when the temperature of the environment exceeds 90 degrees effective temperature.

### CORRELATION OF RECTAL TEMPERATURE AND PULSE RATE TO METABOLIC RATE

An examination of Table 2 will show that whenever more than one sample of expired air was taken in the test chamber at different periods of exposure the heat production invariably increased with the time of exposure. This is to be expected when it is considered that the physiologic reactions vary with temperature and time of exposure. Accordingly, an attempt was made to correlate the rate of metabolism with rectal temperature and with pulse rate in Figures 6 and 7, respectively.

It will be observed that the rate of metabolism correlates fairly well with these two physiologic reactions. In Figure 6 the heat production becomes minimal at a body temperature of about 98.4 degrees F. and it increases both above and below this temperature. It is obvious that metabolism must necessarily increase when there is a drop in body temperature, to keep the body warm. The increase at the higher temperatures is attributed to the warming up of the tissues, which speeds up their chemical activities, and the marked rapid increase for temperatures above 100 degrees is apparently allowed by the breaking down of the human thermostatic control.

Similarly it will be noted that the heat production attains a minimum value of about the same magnitude as shown in the previous figure, namely, 37 calories per square meter per hour, at a pulse rate of 68 beats per minute. Metabolism again increases with higher or lower

pulse rates, but the rate of increase is not as great as it is with change in temperature. A comparison of Figures 6 and 7 shows that the pulse curve is much flatter than that for temperature, indicating that the former is a more dependable direct index of the metabolic rate. The pulse rate increases approximately in direct proportion to the metabolic rate; therefore, the heart works just fast enough to supply the tissues with the extra oxygen needed.

## SUMMARY AND CONCLUSIONS

Dry and wet bulb temperatures (and velocity of air, if any) have been shown to be reducible to one single index called effective temperature. (The charts and tables for determining the effective temperature from the three factors will simplify the study of similar problems.)

The results of these experiments lead to the following conclusions:

1. The rates at which oxygen is consumed and carbon dioxid is produced increase with exposure to either high or low temperatures.

2. There is a zone of minimum metabolic rate between 75 and 83 degrees effective temperature within which basal metabolism should be measured.

3. The metabolic rate increases rapidly when the temperature of the environment is higher than that of the body.

4. Body temperature and pulse rate correlate fairly well with the rate of basal metabolism.

# THE METABOLISM OF OBESITY

## IV. THE DISTRIBUTION OF ENERGY PRODUCTION AFTER FOOD *

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Previous work has shown that there is no demonstrable dependence of obesity upon food intake or caloric balance.[1] Neither can it be proved that any consistent relation exists between constitutional obesity and basal metabolism.[2] It has been shown, however, that these people show a lower specific dynamic action of protein following a high protein intake than normal and thin people.[3] The work here reported was done in conjunction with our investigations on basal metabolism and specific dynamic action of foods. While the figures of this work, based, as they are, on the urinary nitrogen and the nonprotein respiratory quotient, may not be considered as absolutely exact, attention is called to the fact that their relative value is unimpaired because conditions were so well controlled. Each subject served for at least three tests, which were conducted by the same person and under the same conditions except for the type of meal served.

### EXPERIMENTS

Tests were made on obese, thin and normal people, using the same protein, carbohydrate and fat meals described in our previous article.[3] Half an hour before the basal metabolism was taken, the subject was asked to empty the bladder completely. Immediately before the meal, the first urine specimen was collected, and again following each test. The nitrogen content of each specimen was determined by the micro-Kjeldahl method of Folin and Denis.[4] From this the nonprotein

* From the Medical Clinic, the Gusta Morris Rothschild Fund and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Strouse, S., and Dye, M.: Studies on the Metabolism of Obesity. I. The Relation Between Food Intake and Body Weight in Some Obese Persons, Arch. Int. Med. **34**:267 (Sept.) 1924.

2. Strouse, S.; Wang, C. C., and Dye, M.: Studies on the Metabolism of Obesity. II. Basal Metabolism, Arch. Int. Med. **34**:275 (Sept.) 1924.

3. Wang, C. C.; Strouse, S., and Saunders, A. D.: Studies on the Metabolism of Obesity. III. The Specific Dynamic Action of Food, Arch. Int. Med. **34**:573 (Oct.) 1924.

4. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. I. Total Nitrogen in Urine, J. Biol. Chem. **26**:473 (Sept.) 1916.

respiratory quotient for each particular period was determined according to Lusk,[5] and the proportion of carbohydrate and fat used as energy during that period was computed from the table of Zuntz and Schumberg, as modified by Lusk. The calories derived from nitrogen were computed also from Lusk's figures, each gram of urinary nitrogen representing 26.51 calories.

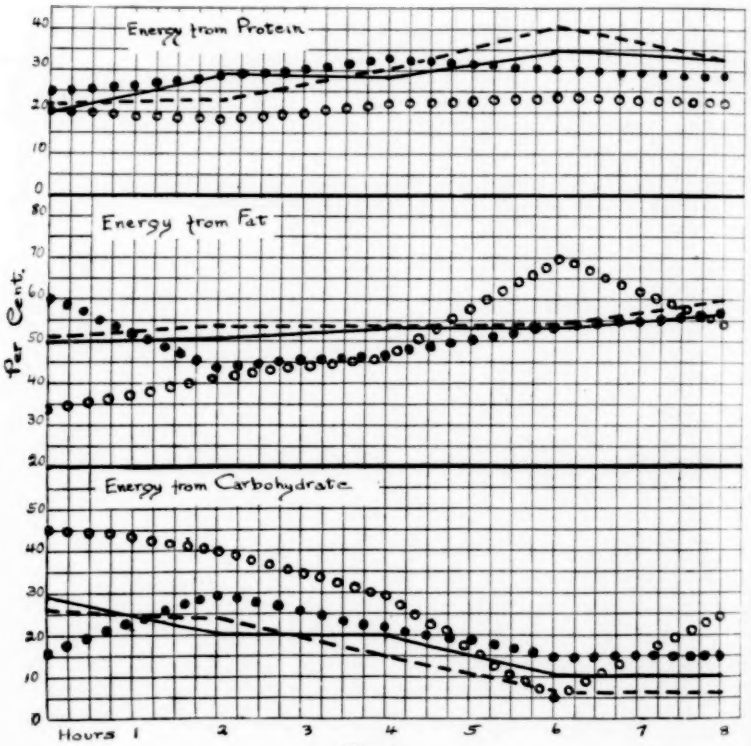


Fig. 1.

Chart 1.—Average percentage distribution of energy production after a high protein meal. Solid dot: overweight, Group 1; open dot: overweight, Group 2; solid line: underweight, and broken line: normal.

Nine obese subjects varying in weight from 37 to 97 per cent. above normal served in eleven tests with the protein meal. With the exception of a 13 year old girl and a 16 year old boy, the subjects were all young women. Their actual weight varied between 76.4 and 118.1 kg.

5. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Company, 1921.

COMMENT

In comparing results of the work with obese people, it will be noted that these can be divided into two distinct groups (Table 1). The first of these, comprising seven people and eight tests, or 78 per cent. of the cases, after the ingestion of a protein meal showed increased energy production from carbohydrate.

In this group the average basal heat production from the carbohydrate was 16 per cent. of the total basal heat production; after two hours it became 29 per cent. of the total; after four hours 22 per cent.; after six hours 15 per cent., and at the end of the eight hour period it was still 15 per cent. of the total calories produced. Group 2, on the other hand, in which three tests were made on two people, showed a decrease in the calories produced from the carbohydrate after the ingestion of a protein meal averaging 46 per cent. of the total basal heat production, followed by 40, 28, 5 and 24 per cent. in the subsequent two hour periods. One of the two subjects in this group on whom two tests were made was not perhaps really obese. She was a girl, aged 13, suffering from gigantism, and was very large for her age but quite solid.

Of the eight thin subjects, only one had increased heat production from carbohydrate or such a slight increase that it was within experimental error. The averages showed a decided decrease from the basal to the end of the experiment, namely, 29, 21, 19, 11 and 11 per cent. in the five periods. The curve for the normal subjects is very much like that for the underweights. Only one of the six tests showed increased energy production over the basal during later periods. The averages were 27 per cent. of the total basal and 24, 15, 6 and 7 per cent. of the total heat production for the four two hour periods.

Table 2 shows an interesting relation between the calories derived from fat and those from carbohydrate. In both groups of obese there is a complementary relation, that is, where the curve for carbohydate goes up that for fat goes down, and vice versa. The first group, which showed an increase in calories derived from carbohydrate, accompanied this by a decrease in calories derived from fat; the second group used fat in place of carbohydrate for energy. The average of calories derived from fat for the first group showed a decrease from 60 per cent. in the basal to 44 per cent. in the first test, and 56 per cent. at the end of the period. The second group showed average values of 34, 42, 47, 70 and 54 per cent. in the respective periods. The underweights and normals, however, showed very little change in the percentage of calories derived from fat from period to period. For the underweights the average figures are 50 per cent. for the basal, 51, 53, 54 and 56 per cent. in the subsequent periods; figures for normals are 51, 53, 54, 53 and 60 per cent.

TABLE 1.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Protein Meal: Calories from Carbohydrate*

| Name | Sex* | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Protein Intake, Gm. | Heat Production: Basal Calories per Hour | Basal Percentage of Total | 2 Hours after Meal Calories per Hour | 2 Hours after Meal Percentage of Total | 4 Hours after Meal Calories per Hour | 4 Hours after Meal Percentage of Total | 6 Hours after Meal Calories per Hour | 6 Hours after Meal Percentage of Total | 8 Hours after Meal Calories per Hour | 8 Hours after Meal Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight, Group 1** | | | | | | | | | | | | | | | | |
| M. N. | ♀ | 29 | 155.0 | 93.6 | +72 | 36.8 | 4 | 7 | 8 | 17 | 5 | 11 | 0 | 0 | 3 | 5 |
| S. A. | ♀ | 25 | 149.5 | 82.3 | +56 | 44.8 | 19 | 29 | 38 | 51 | 14 | 21 | 5 | 8 | 9 | 14 |
| E. S. | ♀ | 34 | 165.0 | 118.1 | +91 | 53.8 | 1 | 1 | 29 | 28 | 3 | 3 | 1 | 1 | 4 | 4 |
| A. D. | ♂ | 16 | 169.5 | 84.6 | +37 | 66.4 | 29 | 37 | 46 | 54 | 62 | 69 | 40 | 48 | 35 | 42 |
| R. K. | ♀ | 26 | 148.5 | 76.4 | +45 | 42.6 | 16 | 22 | 22 | 28 | 20 | 27 | .. | .. | 13 | 17 |
| R. K. | ♀ | 27 | 148.5 | 75.5 | +43 | 46.8 | 11 | 18 | 10 | 15 | 12 | 17 | 22 | 33 | 14 | 22 |
| P. | ♀ | 32 | 171.1 | 103.2 | +58 | 39.1 | 0 | 0 | 10 | 14 | 11 | 14 | 1 | 1 | 3 | 4 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | +42 | 32.0 | 7 | 10 | 13 | 17 | 6 | 9 | .. | .. | .. | .. |
| **Average** | | 27 | 159.0 | 89.9 | +56 | 45.3 | 11 | 16 | 22 | 29 | 17 | 22 | 12 | 15 | 12 | 15 |
| **Overweight, Group 2** | | | | | | | | | | | | | | | | |
| F. P. | ♀ | 34 | 163.8 | 101.2 | +64 | 65.3 | 31 | 39 | 29 | 39 | 18 | 22 | 3 | 4 | 47 | 55 |
| E. M. | ♀ | 13 | 160.5 | 97.8 | +96 | 41.6 | 42 | 53 | 31 | 37 | 16 | 19 | 5 | 6 | 5 | 6 |
| E. M. | ♀ | 13 | 161.5 | 98.6 | +97 | 44.5 | .. | .. | 38 | 43 | 37 | 43 | 3 | 4 | 8 | 10 |
| **Average** | | 30 | 161.9 | 99.2 | +86 | 50.5 | 37 | 46 | 33 | 40 | 24 | 28 | 4 | 5 | 20 | 24 |
| **Underweight** | | | | | | | | | | | | | | | | |
| M. A. | ♀ | 25 | 166.2 | 47.3 | —22 | 35.8 | 20 | 42 | 7 | 12 | 15 | 26 | 5 | 9 | 10 | 21 |
| M. A. | ♀ | 25 | 166.2 | 47.3 | —22 | 64.9 | 15 | 31 | 11 | 20 | 6 | 10 | 7 | 12 | 5 | 9 |
| B. McC. | ♀ | 31 | 170.0 | 47.3 | —28 | 43.9 | 14 | 25 | 22 | 32 | 12 | 17 | 13 | 21 | 9 | 14 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | —31 | 58.2 | 19 | 33 | 14 | 19 | 10 | 14 | 2 | 3 | 0 | 0 |
| B. D. | ♀ | 21 | 159.4 | 41.6 | —26 | 78.3 | 22 | 42 | 5 | 9 | 19 | 32 | 12 | 19 | 13 | 22 |
| Z. O. | ♀ | 24 | 159.4 | 45.0 | —19 | 41.5 | 13 | 26 | 18 | 30 | 17 | 28 | 11 | 20 | 9 | 16 |
| J. W. | ♀ | 35 | 172.5 | 61.4 | —11 | 60.8 | 8 | 13 | 15 | 21 | 14 | 20 | 4 | 6 | 4 | 7 |
| H. B. | ♀ | 19 | 167.6 | 51.0 | —14 | 59.4 | 12 | 22 | 18 | 28 | 2 | 4 | 0 | 0 | 0 | 0 |
| **Average** | | 29 | 166.8 | 48.9 | —22 | 55.3 | 15 | 29 | 14 | 21 | 12 | 19 | 7 | 11 | 6 | 11 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 21 | 167.2 | 62.3 | +3 | 53.5 | 12 | 21 | 28 | 41 | 13 | 18 | 1 | 2 | 3 | 5 |
| M. S. | ♀ | 21 | 167.2 | 61.4 | +2 | 61.1 | 24 | 34 | .. | .. | 15 | 21 | 1 | 2 | 6 | 10 |
| M. W. | ♀ | 24 | 160.0 | 55.5 | +1 | 53.1 | 21 | 32 | 29 | 38 | 26 | 35 | 2 | 3 | 10 | 14 |
| D. K. | ♀ | 22 | 163.5 | 58.6 | +0 | 63.8 | 21 | 36 | 23 | 32 | 6 | 9 | 13 | 19 | 4 | 6 |
| J. S. | ♀ | 21 | 161.0 | 57.7 | +3 | 68.3 | 4 | 7 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 3 |
| E. T. | ♀ | 22 | 163.8 | 54.2 | —7 | 67.1 | 18 | 30 | 7 | 10 | 5 | 8 | 6 | 11 | 3 | 5 |
| **Average** | | 22 | 163.8 | 58.3 | +0.5 | 61.1 | 16 | 27 | 18 | 24 | 11 | 15 | 4 | 6 | 5 | 7 |

* In this and the following tables, ♂ indicates male, ♀ female.

TABLE 2.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Protein Meal: Calories from Fat*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Protein Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 4 Hours after Meal: Calories per Hour | 4 Hours after Meal: Percentage of Total | 6 Hours after Meal: Calories per Hour | 6 Hours after Meal: Percentage of Total | 8 Hours after Meal: Calories per Hour | 8 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight, Group 1** | | | | | | | | | | | | | | | | |
| M. N. | ♀ | 29 | 155.0 | 93.6 | +72 | 36.8 | 39 | 67 | 19 | 41 | 14 | 32 | 21 | 48 | 38 | 62 |
| S. A. | ♀ | 25 | 149.5 | 82.3 | +56 | 44.8 | 35 | 54 | 12 | 16 | 31 | 46 | 39 | 59 | 31 | 49 |
| E. S. | ♀ | 34 | 165.0 | 118.1 | +91 | 53.8 | 87 | 82 | 53 | 52 | 64 | 70 | 77 | 79 | 72 | 74 |
| A. D. | ♂ | 16 | 169.5 | 84.6 | +37 | 66.4 | 35 | 44 | 20 | 24 | 7 | 8 | 21 | 25 | 25 | 30 |
| R. K. | ♀ | 26 | 148.5 | 76.4 | +45 | 42.6 | 34 | 47 | 34 | 43 | 23 | 32 | .. | .. | 32 | 42 |
| R. K. | ♀ | 27 | 148.5 | 75.5 | +43 | 46.8 | 39 | 64 | 42 | 62 | 43 | 61 | 26 | 39 | 36 | 56 |
| P. | ♀ | 32 | 171.1 | 108.2 | +58 | 39.1 | 48 | 67 | 45 | 62 | 47 | 61 | 54 | 73 | 54 | 75 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | +42 | 32.0 | 37 | 55 | 37 | 50 | 42 | 60 | .. | .. | .. | .. |
| Average | | 27 | 159.0 | 89.9 | +56 | 45.3 | 45 | 60 | 33 | 44 | 34 | 47 | 41 | 54 | 41 | 56 |
| **Overweight, Group 2** | | | | | | | | | | | | | | | | |
| F. P. | ♀ | 34 | 163.8 | 101.2 | +64 | 65.3 | 33 | 41 | 39 | 52 | 46 | 51 | 52 | 67 | 17 | 20 |
| E. M. | ♀ | 13 | 160.5 | 97.8 | +96 | 41.6 | 22 | 28 | 32 | 39 | 47 | 56 | 55 | 70 | 57 | 72 |
| E. M. | ♀ | 13 | 161.5 | 98.6 | +96 | 44.5 | .. | .. | 30 | 34 | 29 | 33 | 59 | 74 | 57 | 70 |
| Average | | 20 | 161.9 | 99.2 | +86 | 50.5 | 33 | 34 | 34 | 42 | 41 | 47 | 55 | 70 | 44 | 54 |
| **Underweight** | | | | | | | | | | | | | | | | |
| M. A. | ♀ | 25 | 166.2 | 47.3 | −22 | 35.8 | 15 | 32 | 15 | 25 | 27 | 47 | 28 | 53 | 20 | 42 |
| M. A. | ♀ | 25 | 166.2 | 47.3 | −22 | 64.9 | 24 | 49 | 29 | 53 | 37 | 64 | 31 | 54 | 30 | 57 |
| B. McC. | ♀ | 31 | 170.0 | 47.3 | −28 | 43.9 | 35 | 64 | 35 | 51 | 43 | 61 | 33 | 54 | 39 | 62 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | −31 | 58.2 | 27 | 47 | 43 | 59 | 43 | 58 | 43 | 65 | 49 | 73 |
| B. D. | ♀ | 21 | 159.4 | 41.6 | −26 | 78.3 | 23 | 43 | 40 | 69 | 26 | 44 | 27 | 44 | 29 | 48 |
| Z. O. | ♀ | 24 | 159.4 | 45.0 | −19 | 41.5 | 32 | 62 | 34 | 58 | 33 | 54 | 34 | 61 | 36 | 65 |
| J. W. | ♀ | 35 | 172.5 | 61.4 | −11 | 60.8 | 36 | 57 | 40 | 56 | 32 | 45 | 30 | 50 | 32 | 57 |
| H. B. | ♀ | 19 | 167.6 | 51.0 | −14 | 59.4 | 27 | 50 | 24 | 39 | 30 | 48 | 29 | 48 | 24 | 44 |
| Average | | 29 | 166.8 | 48.9 | −22 | 55.3 | 27 | 50 | 33 | 51 | 34 | 53 | 32 | 54 | 32 | 56 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 21 | 167.2 | 62.3 | +3 | 53.5 | 35 | 60 | 25 | 36 | 40 | 56 | 35 | 51 | 38 | 58 |
| M. S. | ♀ | 21 | 167.2 | 61.4 | +2 | 61.1 | 29 | 47 | .. | .. | 33 | 45 | 32 | 52 | 31 | 53 |
| M. W. | ♀ | 24 | 160.0 | 55.5 | +1 | 53.1 | 32 | 49 | 34 | 45 | 31 | 41 | 45 | 67 | 43 | 61 |
| D. K. | ♀ | 22 | 163.5 | 58.6 | +0 | 63.8 | 28 | 47 | 36 | 51 | 47 | 65 | 31 | 46 | 45 | 68 |
| J. S. | ♀ | 21 | 161.0 | 57.7 | +3 | 68.3 | 39 | 65 | 49 | 71 | 60 | 72 | 41 | 62 | 42 | 67 |
| E. T. | ♀ | 22 | 163.8 | 54.2 | −7 | 67.1 | 22 | 36 | 40 | 60 | 28 | 46 | 23 | 40 | 29 | 51 |
| Average | | 22 | 163.8 | 58.3 | +0.5 | 61.1 | 31 | 51 | 37 | 53 | 40 | 54 | 35 | 53 | 38 | 60 |

TABLE 3.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Protein Meal: Calories from Protein*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Protein Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 4 Hours after Meal: Calories per Hour | 4 Hours after Meal: Percentage of Total | 6 Hours after Meal: Calories per Hour | 6 Hours after Meal: Percentage of Total | 8 Hours after Meal: Calories per Hour | 8 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight, Group 1** | | | | | | | | | | | | | | | | |
| M. N. | ♀ | 29 | 155.0 | 93.6 | +72 | 36.8 | 15 | 26 | 19 | 41 | 25 | 57 | 23 | 52 | 20 | 33 |
| S. A. | ♀ | 25 | 149.5 | 82.3 | +56 | 44.8 | 11 | 17 | 25 | 33 | 23 | 33 | 22 | 33 | 23 | 37 |
| E. S. | ♀ | 34 | 165.0 | 118.1 | +91 | 52.8 | 18 | 17 | 19 | 19 | 25 | 27 | 20 | 20 | 20 | 21 |
| A. D. | ♂ | 16 | 169.5 | 84.6 | +37 | 66.4 | 16 | 20 | 19 | 22 | 21 | 23 | 23 | 27 | 24 | 28 |
| R. K. | ♀ | 26 | 148.5 | 76.4 | +45 | 42.6 | 22 | 31 | 23 | 19 | 30 | 41 | .. | .. | 31 | 41 |
| R. K. | ♀ | 27 | 148.5 | 75.5 | +43 | 46.8 | 11 | 18 | 16 | 24 | 16 | 23 | 19 | 28 | 14 | 22 |
| P. | ♀ | 32 | 171.1 | 103.1 | +58 | 39.1 | 24 | 33 | 18 | 25 | 18 | 24 | 19 | 26 | 15 | 21 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | +42 | 32.0 | 24 | 35 | 24 | 33 | 22 | 31 | .. | .. | .. | .. |
| Average | | 27 | 159.0 | 89.9 | +56 | 45.3 | 18 | 25 | 21 | 29 | 23 | 33 | 21 | 31 | 21 | 29 |
| **Overweight, Group 2** | | | | | | | | | | | | | | | | |
| F. P. | ♀ | 34 | 163.8 | 101.2 | +64 | 65.3 | 16 | 20 | 7 | 9 | 17 | 21 | 21 | 27 | 21 | 25 |
| E. M. | ♀ | 13 | 160.5 | 97.8 | +96 | 41.6 | 16 | 20 | 18 | 21 | 18 | 21 | 18 | 23 | 17 | 22 |
| E. M. | ♀ | 13 | 161.5 | 98.6 | +97 | 44.5 | .. | .. | 20 | 23 | 21 | 24 | 18 | 23 | 16 | 20 |
| Average | | 20 | 161.9 | 99.2 | +86 | 50.5 | 16 | 20 | 15 | 18 | 19 | 22 | 19 | 24 | 18 | 22 |
| **Underweight** | | | | | | | | | | | | | | | | |
| M. A. | ♀ | 25 | 166.2 | 47.3 | —22 | 35.8 | 12 | 26 | 37 | 63 | 15 | 26 | 20 | 38 | 18 | 38 |
| M. A. | ♀ | 25 | 166.2 | 47.3 | —22 | 64.9 | 10 | 20 | 15 | 27 | 15 | 26 | 19 | 33 | 18 | 34 |
| B. McC. | ♀ | 31 | 170.0 | 47.3 | —28 | 43.9 | 6 | 11 | 12 | 17 | 15 | 21 | 15 | 25 | 15 | 24 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | —31 | 58.2 | 11 | 19 | 16 | 22 | 21 | 28 | 21 | 32 | 18 | 27 |
| B. D. | ♀ | 21 | 159.4 | 41.6 | —26 | 78.3 | 8 | 15 | 13 | 22 | 14 | 24 | 23 | 37 | 18 | 30 |
| Z. O. | ♀ | 24 | 159.4 | 45.0 | —19 | 41.5 | 6 | 12 | 7 | 12 | 11 | 19 | 11 | 20 | 10 | 18 |
| J. W. | ♀ | 35 | 172.5 | 61.4 | —11 | 60.8 | 20 | 31 | 16 | 23 | 25 | 35 | 27 | 44 | 20 | 36 |
| H. B. | ♀ | 19 | 167.6 | 51.0 | —14 | 59.4 | 16 | 29 | 21 | 34 | 31 | 49 | 31 | 52 | 30 | 56 |
| Average | | 29 | 166.8 | 48.9 | —22 | 55.3 | 11 | 20 | 17 | 28 | 18 | 29 | 21 | 35 | 18 | 33 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 21 | 167.2 | 62.3 | +3 | 53.5 | 11 | 19 | 16 | 28 | 19 | 26 | 32 | 47 | 24 | 37 |
| M. S. | ♀ | 21 | 167.2 | 61.4 | +2 | 61.1 | 12 | 19 | .. | .. | 25 | 35 | 29 | 47 | 22 | 37 |
| M. W. | ♀ | 24 | 160.0 | 65.5 | +1 | 53.1 | 13 | 17 | 13 | 17 | 18 | 24 | 30 | 30 | 17 | 24 |
| D. K. | ♀ | 22 | 163.5 | 58.6 | +0 | 63.8 | 10 | 17 | 12 | 17 | 19 | 26 | 24 | 35 | 17 | 26 |
| E. T. | ♀ | 22 | 163.8 | 54.2 | —7 | 67.1 | 20 | 34 | 20 | 30 | 29 | 46 | 29 | 49 | 25 | 44 |
| J. S. | ♀ | 21 | 161.0 | 57.7 | +3 | 68.3 | 17 | 28 | 19 | 28 | 22 | 27 | 25 | 38 | 19 | 30 |
| Average | | 22 | 163.8 | 58.5 | +0.5 | 61.1 | 14 | 22 | 16 | 23 | 22 | 31 | 27 | 41 | 21 | 33 |

The actual calories derived from protein, as seen in Table 3, vary little in the two groups of obese subjects. There is likewise little difference in the percentage of calories derived from protein in these groups, varying in the first group between 25 per cent. as a basal and 33 per cent., the highest point four hours later, and in the second group a basal of 20 per cent. with the highest point, 24 per cent., occurring six hours later. Both the underweight subjects and the normals showed a decided rise in the percentage of calories from protein. The average basal percentage of calories from protein for the underweight subjects was

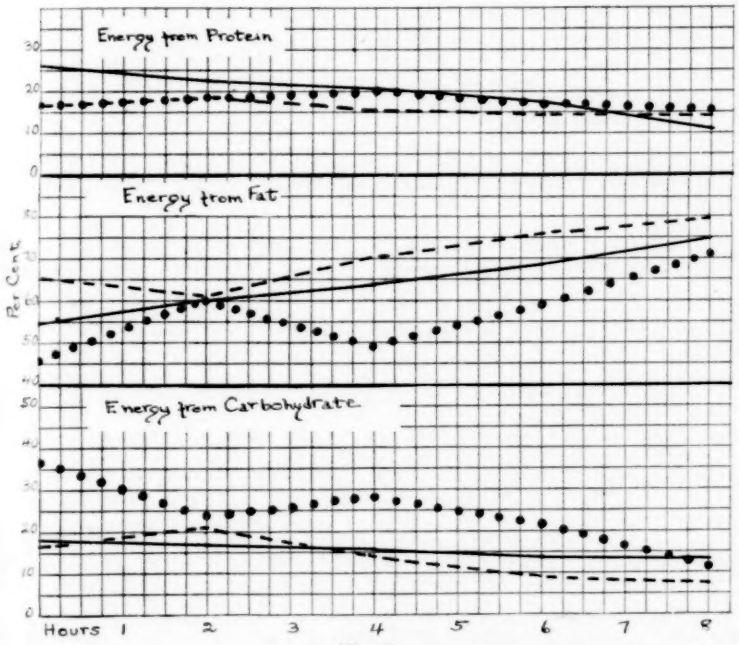


Fig. 2.

Chart 2.—Average percentage distribution of energy production after a high fat meal. Solid dot: overweight; solid line: underweight, and broken line: normal.

20, followed by 28, 29, 35 and 33 per cent. in the subsequent periods. The corresponding basal figures for normals were 22 per cent. and in the following periods 23, 31, 41 and 33 per cent.

The fact that 82 per cent. of the obese cases showed a decided rise in calories derived from carbohydrate and a decrease in calories derived from fat after a high protein meal, and that the thin and normal subjects, on the other hand, utilized protein and fat as their chief sources of

energy, is rather suggestive as to a possible reason for obesity and thinness. The obese conserve the body fat and thus accumulate more, whereas the normal and thin people use up their food fat instead of storing it. On a high protein meal, the normals and the thin people also use much of the protein for energy production but the obese do not. The basal, however, shows that the obese derive most of their energy from fat while on starvation, but the thin and normal have no such store of fat and therefore use up more carbohydrate. Possibly the latter may store more of their carbohydrate as glycogen while the obese convert theirs into fat at once.

Tables 4, 5 and 6 represent what happens after the ingestion of a carbohydrate meal. All subjects used more carbohydrate after the ingestion of 100 gm. of sucrose. The calories derived from carbohydrate during the basal period in obese people was 20 per cent., and the highest percentage, 68, occurred at the end of one hour. The corresponding figures for thin people are 28 per cent. with a peak of 75 per cent. after half an hour. Normals showed a basal of 20 per cent. and 79 per cent. after half an hour.

The percentage of calories derived from fat was decreased in all cases after the carbohydrate meal. In some the use of fat was stopped entirely for one hour, and three of the thin people used no fat after three hours. The three normals all ceased using fat for one hour. There was little difference among the three groups in calories derived from protein after a carbohydrate meal. Most of the cases in all groups had a slight decrease from the basal. The averages for the obese group are 29 per cent. basal, 24, 23, 18 and 18 per cent. in the following periods; figures for the underweights are 25 per cent. basal, followed by 22, 27, 21 and 19 per cent., respectively; those corresponding for normals are 24, 21, 25, 18 and 18 per cent. The continued low use of protein for energy after the carbohydrate meal can be accounted for by the sparing effect of carbohydrate on protein, which is a well established fact.

As might be expected, after the ingestion of a high carbohydrate meal, most of the calories expended as energy were derived from carbohydrate. Even at the end of three hours, most of the subjects were still deriving much more energy from carbohydrate than during the basal period, but still considerably less than at the peak of the curve. This holds for all groups of subjects.

Tables 7, 8 and 9 are concerned with the high fat meal. Calories obtained from carbohydrate after the ingestion of a high fat meal are in most cases decreased from the basal until the end of the eight hour period. The overweight people, on the whole, used more carbohydrate than those of the other two groups, having an average of 37 per cent. for a basal, 24, 28, 22 and 11 per cent. at the end of each of the following

TABLE 4.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Carbohydrate Meal: Calories from Carbohydrate*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Carbohydrate Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | ½ Hour after Meal: Calories per Hour | ½ Hour after Meal: Percentage of Total | 1 Hour after Meal: Calories per Hour | 1 Hour after Meal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 3 Hours after Meal: Calories per Hour | 3 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| A. D. | ♂ | 16 | 169.5 | 82.4 | + 33 | 104.3 | 17 | 23 | 49 | 60 | 42 | 54 | 68 | 80 | 36 | 48 |
| M. S. | ♀ | 33 | 159.5 | 140.0 | +141 | 103.4 | 28 | 32 | 79 | 73 | 75 | 76 | 71 | 70 | 67 | 72 |
| S. A. | ♀ | 25 | 149.5 | 80.0 | + 51 | 106.4 | 4 | 6 | 44 | 56 | 43 | 58 | 47 | 64 | 48 | 67 |
| E. S. | ♀ | 34 | 165.0 | 117.9 | + 90 | 80.2 | 1 | 1 | 13 | 13 | .. | .. | 25 | 25 | 13 | 14 |
| E. S. | ♀ | 28 | 165.0 | 83.6 | + 39 | 100.0 | 13 | 20 | 62 | 75 | 47 | 63 | 62 | 84 | 51 | 74 |
| E. S. | ♀ | 28 | 165.0 | 84.1 | + 40 | 100.0 | 4 | 6 | 58 | 77 | 43 | 59 | 46 | 67 | 32 | 45 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | + 42 | 100.0 | 14 | 18 | 58 | 72 | 53 | 69 | 36 | 50 | 38 | 54 |
| E. S. | ♀ | 28 | 165.0 | 86.3 | + 44 | 100.0 | 19 | 27 | 65 | 78 | 54 | 73 | 51 | 69 | 47 | 67 |
| R. K. | ♀ | 26 | 148.5 | 78.3 | + 48 | 106.2 | 22 | 27 | 36 | 46 | 57 | 65 | 40 | 53 | 26 | 36 |
| E. M. | ♀ | 13 | 161.5 | 100.0 | +102 | 104.5 | 26 | 31 | 79 | 78 | 83 | 83 | 40 | 47 | 32 | 40 |
| F. P. | ♀ | 34 | 163.8 | 101.2 | + 68 | 103.4 | 22 | 32 | 74 | 84 | 66 | 81 | 42 | 55 | 16 | 21 |
| Average | | 27 | 161.6 | 94.5 | + 61 | 100.8 | 15 | 20 | 56 | 65 | 56 | 68 | 48 | 60 | 37 | 49 |
| **Underweight** | | | | | | | | | | | | | | | | |
| S. S. | ♂ | 40 | 174.0 | 51.0 | —30 | 100.0 | 13 | 21 | 41 | 62 | 39 | 59 | 44 | 66 | 31 | 48 |
| K. | ♂ | 25 | 182.0 | 61.4 | —20 | 100.0 | 26 | 41 | 62 | 89 | .. | .. | 50 | 69 | 34 | 55 |
| B. D. | ♀ | 21 | 158.8 | 41.6 | —26 | 107.0 | 18 | 37 | 47 | 82 | 47 | 78 | 54 | 89 | 53 | 90 |
| E. T. | ♀ | 22 | 162.6 | 51.2 | —11 | 102.9 | 13 | 27 | 43 | 76 | 44 | 78 | 46 | 79 | 16 | 33 |
| J. W. | ♀ | 35 | 172.0 | 61.0 | —11 | 103.2 | 23 | 40 | 52 | 75 | 49 | 66 | 50 | 76 | 19 | 36 |
| H. B. | ♀ | 19 | 167.6 | 50.8 | —14 | 105.2 | 9 | 16 | 38 | 65 | 31 | 55 | 29 | 55 | 28 | 56 |
| M. C. | ♀ | 24 | 160.0 | 44.4 | —21 | 105.4 | 8 | 15 | 50 | 79 | 49 | 77 | 52 | 81 | 32 | 61 |
| Average | | 27 | 168.1 | 51.1 | —19 | 103.5 | 16 | 28 | 48 | 75 | 43 | 69 | 46 | 74 | 30 | 54 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W. | ♀ | 24 | 160.0 | 55.5 | —1 | 104.9 | 24 | 39 | 55 | 77 | 52 | 73 | 45 | 65 | 53 | 83 |
| D. K. | ♀ | 22 | 163.5 | 58.2 | —1 | 101.4 | 0 | 0 | 54 | 77 | 48 | 70 | 36 | 55 | 33 | 56 |
| J. S. | ♀ | 21 | 161.3 | 58.2 | +3 | 106.0 | 12 | 20 | 64 | 83 | 61 | 82 | 36 | 55 | 7 | 12 |
| Average | | 22 | 161.6 | 57.3 | +0.3 | 105.0 | 12 | 20 | 58 | 79 | 54 | 78 | 39 | 58 | 31 | 50 |

TABLE 5.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Carbohydrate Meal: Calories from Fat*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Carbohydrate Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | ½ Hour after Meal: Calories per Hour | ½ Hour after Meal: Percentage of Total | 1 Hour after Meal: Calories per Hour | 1 Hour after Meal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 3 Hours after Meal: Calories per Hour | 3 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| A. D. | ♂ | 16 | 169.5 | 82.4 | + 33 | 104.3 | 43 | 50 | 13 | 16 | 18 | 23 | 0 | 0 | 14 | 19 |
| M. S. | ♀ | 33 | 159.5 | 140.0 | +141 | 103.4 | 44 | 50 | 0 | 0 | 9 | 9 | 5 | 5 | 14 | 15 |
| S. A. | ♀ | 25 | 149.5 | 80.0 | + 51 | 106.4 | 48 | 67 | 11 | 14 | 16 | 22 | 15 | 21 | 15 | 21 |
| E. S. | ♀ | 34 | 165.0 | 117.8 | + 90 | 80.2 | 77 | 81 | 56 | 74 | .. | .. | 64 | 65 | 68 | 73 |
| E. S. | ♀ | 28 | 165.0 | 83.6 | + 39 | 100.0 | 21 | 33 | 0 | 0 | 7 | 9 | 2 | 3 | 10 | 15 |
| E. S. | ♀ | 28 | 165.0 | 84.1 | + 40 | 100.0 | 46 | 65 | 0 | 0 | 7 | 9 | 9 | 13 | 29 | 41 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | + 42 | 100.0 | 35 | 46 | 0 | 0 | 0 | 0 | 21 | 29 | 20 | 29 |
| E. S. | ♀ | 28 | 165.0 | 86.3 | + 44 | 100.0 | 31 | 43 | 0 | 0 | 0 | 0 | 11 | 15 | 12 | 17 |
| R. K. | ♀ | 26 | 148.5 | 78.3 | + 48 | 106.2 | 31 | 38 | 13 | 17 | 14 | 16 | 18 | 24 | 30 | 41 |
| E. M. | ♀ | 13 | 161.5 | 100.0 | +102 | 104.5 | 35 | 42 | 0 | 0 | 0 | 0 | 28 | 33 | 34 | 43 |
| F. P. | ♀ | 34 | 163.8 | 101.2 | + 68 | 103.4 | 27 | 39 | 0 | 0 | 0 | 0 | 21 | 27 | 47 | 61 |
| Average | | 27 | 161.6 | 94.5 | + 63 | 100.8 | 40 | 51 | 10 | 11 | 7 | 9 | 18 | 21 | 27 | 34 |
| **Underweight** | | | | | | | | | | | | | | | | |
| S. S. | ♂ | 40 | 174.0 | 51.0 | —30 | 100.0 | 31 | 52 | 10 | 15 | 6 | 9 | 8 | 12 | 21 | 32 |
| K. | ♂ | 25 | 182.0 | 61.4 | —20 | 100.0 | 21 | 33 | 2 | 3 | .. | .. | 0 | 0 | 18 | 29 |
| B. D. | ♀ | 21 | 158.8 | 41.6 | —26 | 107.0 | 22 | 46 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E. T. | ♀ | 22 | 162.6 | 51.2 | —11 | 102.9 | 23 | 46 | 0 | 0 | 0 | 0 | 0 | 0 | 21 | 45 |
| J. W. | ♀ | 35 | 172.0 | 61.0 | —11 | 103.2 | 17 | 30 | 0 | 0 | 6 | 8 | 0 | 0 | 21 | 39 |
| H. B. | ♀ | 19 | 167.6 | 50.8 | —14 | 105.2 | 32 | 50 | 0 | 0 | 5 | 9 | 13 | 24 | 12 | 23 |
| M. C. | ♀ | 24 | 160.0 | 44.4 | —21 | 105.4 | 34 | 62 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 18 |
| Average | | 27 | 168.1 | 51.6 | —19 | 103.5 | 26 | 47 | 2 | 3 | 3 | 4 | 3 | 5 | 15 | 27 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W | ♀ | 24 | 160.0 | 55.5 | —1 | 104.9 | 19 | 31 | 0 | 0 | 0 | 0 | 11 | 16 | 0 | 0 |
| D. K. | ♀ | 22 | 163.5 | 58.2 | —1 | 104.4 | 42 | 78 | 0 | 0 | 0 | 0 | 19 | 29 | 14 | 24 |
| J. S. | ♀ | 21 | 161.3 | 58.2 | +3 | 106.0 | 36 | 60 | 0 | 0 | 0 | 0 | 19 | 29 | 42 | 70 |
| Average | | 22 | 161.6 | 57.3 | +0.3 | 105.0 | 32 | 56 | 0 | 0 | 0 | 0 | 16 | 25 | 19 | 31 |

TABLE 6.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Carbohydrate Meal: Calories from Protein*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Carbohydrate Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | ½ Hour after Meal: Calories per Hour | ½ Hour after Meal: Percentage of Total | 1 Hour after Meal: Calories per Hour | 1 Hour after Meal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 3 Hours after Meal: Calories per Hour | 3 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| A. D. | ♂ | 16 | 169.5 | 82.4 | + 33 | 104.3 | 13 | 18 | 19 | 24 | 18 | 23 | 17 | 20 | 25 | 33 |
| M. S. | ♀ | 33 | 159.5 | 140.0 | +141 | 103.4 | 16 | 18 | 29 | 27 | 15 | 15 | 25 | 25 | 15 | 16 |
| S. A. | ♀ | 25 | 149.5 | 80.0 | + 51 | 106.4 | 20 | 28 | 23 | 30 | 15 | 20 | 11 | 15 | 9 | 13 |
| E. S. | ♀ | 34 | 165.0 | 117.8 | + 90 | 80.2 | 17 | 18 | 13 | 13 | .. | .. | 10 | 10 | 12 | 13 |
| E. S. | ♀ | 28 | 165.0 | 83.6 | + 39 | 100.0 | 30 | 47 | 21 | 25 | 21 | 28 | 10 | 14 | 8 | 12 |
| E. S. | ♀ | 28 | 165.0 | 84.1 | + 40 | 100.0 | 21 | 30 | 17 | 23 | 22 | 31 | 14 | 20 | 10 | 14 |
| E. S. | ♀ | 28 | 165.0 | 85.5 | + 42 | 100.0 | 27 | 36 | 23 | 28 | 24 | 31 | 15 | 21 | 12 | 17 |
| E. S. | ♀ | 28 | 165.0 | 86.3 | + 44 | 100.0 | 21 | 30 | 18 | 22 | 20 | 27 | 12 | 16 | 11 | 16 |
| R. K. | ♀ | 26 | 148.5 | 78.3 | + 48 | 106.2 | 28 | 35 | 29 | 37 | 17 | 19 | 18 | 24 | 17 | 23 |
| E. M. | ♀ | 13 | 161.5 | 100.0 | +102 | 104.5 | 22 | 27 | 23 | 23 | 17 | 17 | 17 | 20 | 14 | 18 |
| F. P. | ♀ | 34 | 163.8 | 101.2 | + 68 | 103.4 | 20 | 29 | 14 | 16 | 15 | 19 | 14 | 18 | 14 | 18 |
| Average | | 27 | 161.6 | 94.5 | + 63 | 100.8 | 21 | 29 | 21 | 24 | 18 | 23 | 15 | 18 | 13 | 18 |
| **Underweight** | | | | | | | | | | | | | | | | |
| S. S. | ♂ | 40 | 174.0 | 51.0 | −30 | 100.0 | 16 | 27 | 15 | 23 | 21 | 32 | 16 | 24 | 12 | 18 |
| K. | ♂ | 25 | 182.0 | 61.4 | −20 | 100.0 | 16 | 25 | 5 | 7 | .. | .. | 22 | 31 | 10 | 16 |
| B. D. | ♀ | 21 | 158.8 | 41.6 | −26 | 107.0 | 8 | 17 | 10 | 18 | 13 | 22 | 7 | 11 | 6 | 10 |
| E. T. | ♀ | 22 | 162.6 | 51.2 | −11 | 102.9 | 13 | 27 | 13 | 24 | 13 | 22 | 12 | 21 | 10 | 22 |
| J. W. | ♀ | 35 | 172.0 | 61.0 | −11 | 103.2 | 17 | 30 | 18 | 26 | 19 | 26 | 16 | 24 | 14 | 26 |
| H. B. | ♀ | 19 | 167.6 | 50.8 | −14 | 105.2 | 14 | 25 | 20 | 35 | 20 | 36 | 11 | 21 | 10 | 21 |
| M. C. | ♀ | 24 | 160.0 | 44.4 | −21 | 105.4 | 12 | 23 | 13 | 21 | 14 | 23 | 12 | 19 | 12 | 22 |
| Average | | 27 | 168.1 | 51.6 | −19 | 103.5 | 14 | 25 | 13 | 22 | 17 | 27 | 14 | 21 | 11 | 19 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W. | ♀ | 24 | 160.0 | 55.5 | −1 | 104.9 | 18 | 30 | 16 | 23 | 19 | 27 | 13 | 19 | 11 | 17 |
| D. K. | ♀ | 22 | 163.5 | 58.2 | −1 | 104.4 | 12 | 22 | 16 | 23 | 21 | 30 | 11 | 17 | 12 | 20 |
| J. S. | ♀ | 21 | 161.3 | 58.2 | +3 | 106.0 | 12 | 20 | 13 | 17 | 13 | 18 | 11 | 17 | 11 | 18 |
| Average | | 22 | 161.6 | 57.3 | +0.3 | 105.0 | 14 | 24 | 15 | 21 | 18 | 25 | 12 | 18 | 11 | 18 |

two hour periods. Corresponding averages for underweight people are 18, 17, 16, 14 and 13 per cent., and for normal 17, 21, 14, 9 and 7 per cent. Here again the obese people seem to tend to use their carbohydrate for energy and to store the fat, but the normal and thin people use up the fat ingested to produce heat.

All groups showed an increase in energy derived from fat after the ingestion of a high fat meal. The greatest increase, however, is found

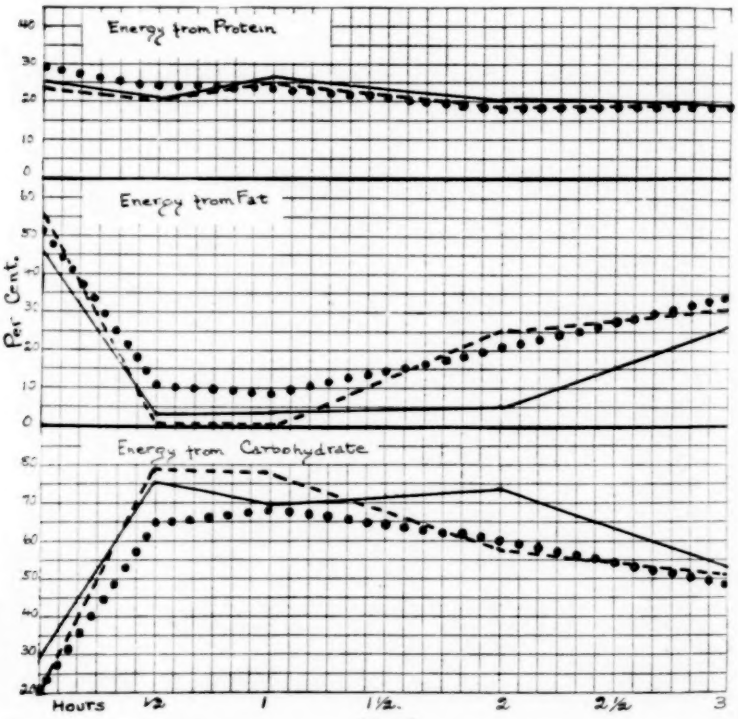


Fig. 3.

Chart 3.—Average percentage distribution of energy production after a high carbohydrate meal. Solid dot: overweight; solid line: underweight, and broken line: normal.

in the thin and in the normal groups. Average basal values for the obese are 46 per cent., followed by 60, 49, 59 and 71 per cent. after each two hour period; for underweights 55, 60, 64, 68 and 75 per cent., and corresponding figures for normals, 66, 61, 71, 77 and 79 per cent.

Energy derived from protein is very little affected by the ingestion of a high fat meal in the three groups, and especially in the case of the

TABLE 7.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Fat Meal: Calories from Carbohydrate*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Fat Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 4 Hours after Meal: Calories per Hour | 4 Hours after Meal: Percentage of Total | 6 Hours after Meal: Calories per Hour | 6 Hours after Meal: Percentage of Total | 8 Hours after Meal: Calories per Hour | 8 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 33 | 159.5 | 131.5 | +136 | 54.7 | 40 | 41 | 22 | 23 | 23 | 23 | 28 | 29 | 1 | 1 |
| A. D. | ♂ | 16 | 169.5 | 83.7 | + 35 | 109.0 | 28 | 39 | 19 | 24 | 26 | 32 | 16 | 21 | 15 | 18 |
| A. D. | ♂ | 16 | 169.5 | 87.7 | + 46 | 82.8 | 25 | 32 | 20 | 24 | 24 | 29 | 14 | 17 | 13 | 15 |
| E. M. | ♀ | 13 | 161.5 | 98.6 | + 99 | 129.1 | 12 | 14 | 12 | 15 | 11 | 13 | 1 | 1 | 6 | 8 |
| Average | | 19 | 165.0 | 100.3 | + 79 | 93.9 | 26 | 37 | 18 | 24 | 21 | 28 | 15 | 22 | 9 | 11 |
| **Underweight** | | | | | | | | | | | | | | | | |
| B. D. | ♀ | 21 | 150.1 | 41.5 | —26 | 50.7 | 15 | 31 | 22 | 42 | 19 | 37 | 18 | 32 | 9 | 17 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | —31 | 53.3 | 13 | 21 | 22 | 32 | 10 | 16 | 8 | 13 | 5 | 8 |
| H. B. | ♀ | 19 | 167.6 | 50.7 | —15 | 55.3 | 4 | 7 | 4 | 7 | 8 | 15 | 1 | 2 | 7 | 13 |
| E. T. | ♀ | 22 | 163.1 | 50.8 | —11 | 76.1 | 8 | 15 | 11 | 19 | 13 | 23 | 9 | 17 | 15 | 27 |
| M. C. | ♀ | 24 | 160.3 | 44.5 | —20 | 39.9 | 13 | 25 | 1 | 2 | 0 | 0 | 10 | 17 | 6 | 11 |
| J. W. | ♀ | 35 | 172.0 | 61.7 | —10 | 78.9 | 6 | 10 | 0 | 0 | 3 | 5 | 3 | 5 | 2 | 3 |
| Average | | 27 | 166.4 | 49.9 | —19 | 50.0 | 10 | 18 | 10 | 17 | 9 | 16 | 7 | 14 | 7 | 13 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W. | ♀ | 24 | 160.0 | 55.0 | —2 | 79.8 | 18 | 30 | 13 | 20 | 17 | 27 | 8 | 12 | 14 | 22 |
| D. K. | ♀ | 22 | 163.5 | 58.2 | +2 | 84.5 | 11 | 19 | 27 | 44 | 6 | 10 | 2 | 3 | 0 | 0 |
| J. S. | ♀ | 21 | 160.3 | 57.2 | +2 | 55.0 | 1 | 2 | 0 | 0 | 3 | 5 | 7 | 11 | 0 | 0 |
| Average | | 22 | 161.3 | 56.8 | +1 | 73.1 | 10 | 17 | 13 | 21 | 9 | 14 | 6 | 9 | 5 | 7 |

TABLE 8.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Fat Meal: Calories from Fat*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Fat Intake, Gm. | Heat Production: Basal: Calories per Hour | Basal: Percentage of Total | 2 Hours after Meal: Calories per Hour | 2 Hours after Meal: Percentage of Total | 4 Hours after Meal: Calories per Hour | 4 Hours after Meal: Percentage of Total | 6 Hours after Meal: Calories per Hour | 6 Hours after Meal: Percentage of Total | 8 Hours after Meal: Calories per Hour | 8 Hours after Meal: Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 33 | 150.5 | 131.3 | +136 | 54.7 | 47 | 48 | 64 | 67 | 57 | 57 | 52 | 54 | 75 | 83 |
| A. D. | ♂ | 16 | 169.5 | 83.7 | + 35 | 109.0 | 29 | 41 | 42 | 58 | 35 | 44 | 48 | 62 | 52 | 63 |
| A. D. | ♂ | 16 | 169.5 | 87.7 | + 46 | 82.8 | 39 | 50 | 49 | 60 | 38 | 46 | 51 | 61 | 58 | 68 |
| E. M. | ♀ | 13 | 161.5 | 98.6 | + 99 | 129.1 | 55 | 65 | 52 | 63 | 64 | 77 | 72 | 87 | 65 | 80 |
| Average | | 19 | 165.0 | 100.3 | + 79 | 93.9 | 43 | 46 | 52 | 60 | 49 | 49 | 56 | 59 | 63 | 71 |
| **Underweight** | | | | | | | | | | | | | | | | |
| B. D | ♀ | 21 | 159.1 | 41.5 | —26 | 50.7 | 20 | 41 | 16 | 30 | 23 | 45 | 28 | 50 | 38 | 72 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | —31 | 53.3 | 34 | 56 | 31 | 46 | 38 | 60 | 43 | 67 | 50 | 76 |
| H. B. | ♀ | 19 | 167.6 | 50.7 | —15 | 55.3 | 34 | 64 | 37 | 68 | 35 | 63 | 44 | 81 | 41 | 72 |
| E. T. | ♀ | 22 | 163.1 | 50.8 | —11 | 76.1 | 32 | 60 | 32 | 57 | 32 | 57 | 33 | 63 | 31 | 54 |
| M. C. | ♀ | 24 | 160.3 | 44.5 | —20 | 39.9 | 27 | 53 | 43 | 78 | 46 | 81 | 41 | 70 | 49 | 81 |
| J. W. | ♀ | 35 | 172.0 | 61.7 | —10 | 78.9 | 32 | 58 | 49 | 79 | 51 | 79 | 51 | 80 | 53 | 94 |
| Average | | 27 | 166.4 | 49.9 | —19 | 59.0 | 30 | 55 | 35 | 60 | 37 | 64 | 40 | 68 | 44 | 75 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W. | ♀ | 24 | 160.0 | 55.0 | —2 | 79.8 | 29 | 48 | 39 | 61 | 36 | 58 | 48 | 73 | 42 | 65 |
| D. K. | ♀ | 22 | 163.5 | 58.2 | +2 | 84.5 | 38 | 65 | 22 | 36 | 44 | 72 | 47 | 78 | 45 | 79 |
| J. S. | ♀ | 21 | 160.3 | 57.2 | +2 | 55.0 | 51 | 85 | 55 | 85 | 52 | 84 | 52 | 81 | 53 | 93 |
| Average | | 22 | 161.3 | 56.8 | +1 | 73.1 | 39 | 66 | 39 | 61 | 44 | 71 | 49 | 77 | 47 | 79 |

TABLE 9.—*Distribution of Total Energy Between Protein, Fat and Carbohydrate After High Fat Meal: Calories from Protein*

| Name | Sex | Age | Height, Cm. | Weight: Kilograms | Weight: Percentage of Difference from Normal | Fat Intake, Gm. | Heat Production: Basal Calories per Hour | Basal Percentage of Total | 2 Hours after Meal Calories per Hour | 2 Hours after Meal Percentage of Total | 4 Hours after Meal Calories per Hour | 4 Hours after Meal Percentage of Total | 6 Hours after Meal Calories per Hour | 6 Hours after Meal Percentage of Total | 8 Hours after Meal Calories per Hour | 8 Hours after Meal Percentage of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Overweight** | | | | | | | | | | | | | | | | |
| M. S. | ♀ | 33 | 150.5 | 131.3 | +136 | 54.7 | 10 | 10 | 10 | 10 | 21 | 21 | 17 | 18 | 14 | 16 |
| A. D. | ♂ | 16 | 169.5 | 83.7 | + 35 | 109.0 | 14 | 20 | 18 | 23 | 19 | 23 | 13 | 17 | 15 | 18 |
| A. D | ♂ | 16 | 169.5 | 87.7 | + 46 | 82.8 | 14 | 18 | 13 | 16 | 21 | 26 | 18 | 22 | 14 | 16 |
| E. M. | ♀ | 12 | 161.5 | 98.6 | + 99 | 129.1 | 18 | 21 | 18 | 22 | 8 | 10 | 10 | 12 | 10 | 12 |
| **Average** | | 19 | 165.0 | 100.3 | + 79 | 93.9 | 14 | 17 | 15 | 18 | 17 | 20 | 15 | 17 | 13 | 16 |
| **Underweight** | | | | | | | | | | | | | | | | |
| B. D. | ♀ | 21 | 159.1 | 41.5 | —26 | 50.7 | 14 | 29 | 15 | 28 | 9 | 18 | 10 | 18 | 6 | 11 |
| S. S. | ♂ | 42 | 173.4 | 50.2 | —31 | 53.3 | 14 | 23 | 15 | 22 | 15 | 24 | 14 | 22 | 11 | 17 |
| H. B. | ♀ | 19 | 167.6 | 50.7 | —15 | 55.3 | 16 | 29 | 14 | 25 | 13 | 23 | 9 | 17 | 9 | 15 |
| E. T. | ♀ | 22 | 163.1 | 50.8 | —11 | 76.1 | 13 | 25 | 14 | 24 | 11 | 20 | 11 | 21 | 11 | 19 |
| M. C. | ♀ | 24 | 160.3 | 44.5 | —20 | 39.9 | 11 | 22 | 11 | 20 | 11 | 19 | 8 | 13 | 5 | 8 |
| J. W. | ♀ | 35 | 172.0 | 61.7 | —10 | 78.9 | 17 | 31 | 13 | 21 | 10 | 16 | 5 | 8 | 2 | 3 |
| **Average** | | 27 | 166.4 | 49.9 | —19 | 59.0 | 14 | 27 | 14 | 23 | 11 | 20 | 9 | 17 | 7 | 12 |
| **Normal** | | | | | | | | | | | | | | | | |
| M. W. | ♀ | 24 | 160.0 | 55.0 | —2 | 79.8 | 14 | 23 | 12 | 19 | 9 | 15 | 10 | 15 | 9 | 14 |
| D. K | ♀ | 22 | 163.5 | 58.2 | +2 | 84.5 | 9 | 16 | 12 | 20 | 11 | 18 | 11 | 18 | 12 | 21 |
| J. S | ♀ | 21 | 160.3 | 57.2 | +2 | 55.0 | 8 | 13 | 10 | 15 | 7 | 11 | 5 | 8 | 4 | 7 |
| **Average** | | 22 | 161.3 | 56.8 | +1 | 73.1 | 10 | 17 | 11 | 18 | 9 | 15 | 9 | 14 | 8 | 14 |

TABLE 10.—*The Respiratory Quotient of Obese, Thin and Normal People After the Ingestion of Protein, Carbohydrate and Fat*

| Subject | Percentage of Variation from Normal Weight | Respiratory Quotient: Basal | | | 1* | | | 2 | | | 3 | | | 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Protein | Carbohydrate | Fat | Protein | Carbohydrate | Fat | Protein | Carbohydrate | Fat | Protein | Carbohydrate | Fat | Protein | Carbohydrate | Fat |
| | | | | | | | | Overweight | | | | | | | | |
| M. N. | +72 | 0.75 | ..... | ..... | 0.79 | ..... | ..... | 0.80 | ..... | ..... | 0.74 | ..... | ..... | 0.76 | ..... | ..... |
| S. A. | +56 | 0.808 | ..... | ..... | 0.883 | ..... | ..... | 0.805 | ..... | ..... | 0.760 | ..... | ..... | 0.782 | ..... | ..... |
| | +51 | ..... | 0.754 | ..... | ..... | 0.809 | ..... | ..... | 0.804 | ..... | ..... | 0.908 | ..... | ..... | 0.914 | ..... |
| E. S. | +91 | 0.732 | ..... | ..... | 0.806 | ..... | ..... | 0.743 | ..... | ..... | 9.726 | ..... | ..... | 0.738 | ..... | ..... |
| | +90 | ..... | 0.725 | ..... | ..... | 0.758 | ..... | ..... | ..... | ..... | ..... | 0.794 | ..... | ..... | 0.762 | ..... |
| A. D. | +37 | 0.836 | ..... | ..... | 0.888 | ..... | ..... | 0.923 | ..... | ..... | 0.874 | ..... | ..... | 0.855 | ..... | ..... |
| | +33 | ..... | 0.782 | ..... | ..... | 0.908 | ..... | ..... | 0.884 | ..... | ..... | 0.973 | ..... | ..... | 0.877 | ..... |
| | +35 | ..... | ..... | 0.837 | ..... | ..... | 0.803 | ..... | ..... | 0.833 | ..... | ..... | 0.782 | ..... | ..... | 0.789 |
| | +46 | ..... | ..... | 0.817 | ..... | ..... | 0.793 | ..... | ..... | 0.815 | .. .. | ..... | 0.779 | ..... | ..... | 0.772 |
| R. K. | +45 | 0.80 | ..... | ..... | 0.81 | ..... | ..... | 0.83 | ..... | ..... | 0.77 | ..... | ..... | 0.80 | ..... | ..... |
| | +43 | 0.772 | ..... | ..... | 0.775 | ..... | ..... | 0.776 | ..... | ..... | 0.829 | ..... | ..... | 0.789 | ..... | ..... |
| | +48 | ..... | 0.819 | ..... | ..... | 0.874 | ..... | ..... | 0.919 | ..... | ..... | 0.890 | ..... | ..... | 0.830 | ..... |
| P. | +58 | 0.680 | ..... | ..... | 0.773 | ..... | ..... | 0.770 | ..... | ..... | 0.741 | ..... | ..... | 0.737 | ..... | ..... |
| S. | +42 | 0.78 | ..... | ..... | 0.80 | ..... | ..... | 0.79 | ..... | ..... | 0.77 | ..... | ..... | 0.76 | ..... | ..... |
| | +39 | ..... | 0.81 | ..... | ..... | 0.98 | ..... | ..... | 0.91 | ..... | ..... | 0.97 | ..... | ..... | 0.93 | ..... |
| | +40 | ..... | 0.76 | ..... | ..... | 0.97 | ..... | ..... | 0.91 | ..... | ..... | 0.88 | ..... | ..... | 0.85 | ..... |
| | +42 | ..... | 0.80 | ..... | ..... | 0.94 | ..... | ..... | 0.97 | ..... | ..... | 0.87 | ..... | ..... | 0.88 | ..... |
| | +44 | ..... | 0.82 | ..... | ..... | 1.02 | ..... | ..... | 0.96 | ..... | ..... | 0.92 | ..... | ..... | 0.91 | ..... |
| F. P. | +64 | 0.838 | ..... | ..... | 0.831 | ..... | ..... | 0.793 | ..... | ..... | 0.749 | ..... | ..... | 0.848 | ..... | ..... |
| | +68 | ..... | 0.829 | ..... | ..... | 0.971 | ..... | ..... | 0.980 | ..... | ..... | 0.878 | ..... | ..... | 0.783 | ..... |
| E. M. | +96 | 0.880† | ..... | ..... | 0.840 | ..... | ..... | 0.786 | ..... | ..... | 0.746 | ..... | ..... | 0.747 | ..... | ..... |
| | +97 | ..... | ..... | ..... | 0.853 | ..... | ..... | 0.854 | ..... | ..... | 0.742 | ..... | ..... | 0.753 | ..... | ..... |
| | +96 | ..... | 0.825 | ..... | ..... | 1.040 | ..... | ..... | 0.976 | ..... | ..... | 0.867 | ..... | ..... | 0.839 | ..... |
| | +99 | ..... | ..... | 0.802 | ..... | ..... | 0.774 | ..... | ..... | 0.760 | ..... | ..... | 0.722 | ..... | ..... | 0.744 |
| M. S. | +141 | ..... | 0.817 | ..... | ..... | 0.968 | ..... | ..... | 0.945 | ..... | ..... | 0.934 | ..... | ..... | 0.924 | ..... |
| | +136 | ..... | ..... | 0.852 | ..... | ..... | 0.777 | ..... | ..... | 0.793 | ..... | ..... | 0.812 | ..... | ..... | 0.722 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Underweight | | | | | | | | | |
| Z. O. ..... | −19 | 0.796 | ..... | ..... | 0.810 | ..... | ..... | 0.808 | ..... | ..... | 0.786 | ..... | ..... | 0.774 | ..... | ..... |
| J. W. ..... | −11 | 0.776 | ..... | ..... | 0.794 | ..... | ..... | 0.802 | ..... | ..... | 0.772 | ..... | ..... | 0.764 | ..... | ..... |
| | −11 | ..... | 0.853 | ..... | ..... | 1.087 | ..... | ..... | 0.925 | ..... | ..... | 0.958 | ..... | ..... | 0.838 | ..... |
| | −10 | ..... | ..... | 0.771 | ..... | ..... | 0.714 | ..... | ..... | 0.738 | ..... | ..... | 0.733 | ..... | ..... | 0.721 |
| H. B. ..... | −14 | 0.780 | ..... | ..... | 0.822 | ..... | ..... | 0.769 | ..... | ..... | 0.742 | ..... | ..... | 0.756 | ..... | ..... |
| | −14 | ..... | 0.780 | ..... | ..... | 0.962 | ..... | ..... | 0.901 | ..... | ..... | 0.800 | ..... | ..... | 0.800 | ..... |
| | −15 | ..... | ..... | 0.758 | ..... | ..... | 0.752 | ..... | ..... | 0.766 | ..... | ..... | 0.732 | ..... | ..... | 0.761 |
| S. S. ..... | −31 | 0.823 | ..... | ..... | 0.788 | ..... | ..... | 0.774 | ..... | ..... | 0.749 | ..... | ..... | 0.724 | ..... | ..... |
| | −30 | ..... | 0.79 | ..... | ..... | 0.91 | ..... | ..... | 0.90 | ..... | ..... | 0.91 | ..... | ..... | 0.87 | ..... |
| | −31 | ..... | ..... | 0.789 | ..... | ..... | 0.828 | ..... | ..... | 0.785 | ..... | ..... | 0.763 | ..... | ..... | 0.745 |
| B. D. ..... | −26 | 0.843 | ..... | ..... | 0.753 | ..... | ..... | 0.822 | ..... | ..... | 0.798 | ..... | ..... | 0.804 | ..... | ..... |
| | −26 | ..... | 0.838 | ..... | ..... | 1.055 | ..... | ..... | 1.040 | ..... | ..... | 1.013 | ..... | ..... | 1.031 | ..... |
| | −26 | ..... | ..... | 0.820 | ..... | ..... | 0.857 | ..... | ..... | 0.829 | ..... | ..... | 0.813 | ..... | ..... | 0.766 |
| E. T. ..... | −11 | ..... | 0.814 | ..... | ..... | 1.023 | ..... | ..... | 0.987 | ..... | ..... | 1.048 | ..... | ..... | 0.827 | ..... |
| | −11 | ..... | ..... | 0.777 | ..... | ..... | 0.789 | ..... | ..... | 0.796 | ..... | ..... | 0.778 | ..... | ..... | 0.806 |
| M. C. ..... | −21 | ..... | 0.775 | ..... | ..... | 1.033 | ..... | ..... | 1.028 | ..... | ..... | 0.964 | ..... | ..... | 0.905 | ..... |
| | −20 | ..... | ..... | 0.804 | ..... | ..... | 0.730 | ..... | ..... | 0.716 | ..... | ..... | 0.772 | ..... | ..... | 0.748 |
| A. K. ..... | −20 | ..... | 0.86 | ..... | ..... | 0.97 | ..... | ..... | 0.83 | ..... | ..... | 0.96 | ..... | ..... | 0.89 | ..... |
| M. A. ..... | −22 | 0.85 | ..... | ..... | 0.80 | ..... | ..... | 0.81 | ..... | ..... | 0.77 | ..... | ..... | 0.80 | ..... | ..... |
| | −22 | 0.82 | ..... | ..... | 0.79 | ..... | ..... | 0.77 | ..... | ..... | 0.77 | ..... | ..... | 0.77 | ..... | ..... |
| B. M. ..... | −28 | 0.80 | ..... | ..... | 0.82 | ..... | ..... | 0.78 | ..... | ..... | 0.80 | ..... | .... | 0.77 | ..... | ..... |
| | | | | | | | | Normal | | | | | | | | | |
| M. W. ..... | +1 | 0.816 | ..... | ..... | 0.836 | ..... | ..... | 0.833 | ..... | ..... | 0.745 | ..... | ..... | 0.763 | ..... | ..... |
| | −1 | ..... | 0.846 | ..... | ..... | 1.036 | ..... | ..... | 0.988 | ..... | ..... | 0.914 | ..... | ..... | 0.970 | ..... |
| | −2 | ..... | ..... | 0.813 | ..... | ..... | 0.787 | ..... | ..... | 0.798 | ..... | ..... | 0.759 | ..... | ..... | 0.779 |
| D. K. ..... | +0 | 0.827 | ..... | ..... | 0.817 | ..... | ..... | 0.757 | ..... | ..... | 0.788 | ..... | ..... | 0.754 | ..... | ..... |
| | −1 | ..... | 0.717 | ..... | ..... | 1.050 | ..... | ..... | 0.970 | ..... | ..... | 0.881 | ..... | ..... | 0.888 | ..... |
| | +2 | ..... | ..... | 0.775 | ..... | ..... | 0.852 | ..... | ..... | 0.750 | ..... | ..... | 0.737 | ..... | ..... | 0.707 |
| J. S. ..... | +3 | 0.753 | ..... | ..... | 0.739 | ..... | ..... | 0.737 | ..... | ..... | 0.732 | ..... | ..... | 0.749 | ..... | ..... |
| | +3 | ..... | 0.786 | ..... | ..... | 1.005 | ..... | ..... | 0.959 | ..... | ..... | 0.883 | ..... | ..... | 0.758 | ..... |
| | +2 | ..... | ..... | 0.720 | ..... | ..... | 0.694 | ..... | ..... | 0.726 | ..... | ..... | 0.748 | ..... | ..... | 0.656 |
| M. S. ..... | +3 | 0.79 | ..... | ..... | 0.84 | ..... | ..... | 0.79 | ..... | ..... | 0.76 | ..... | ..... | 0.76 | ..... | ..... |
| | +2 | 0.824 | ..... | ..... | ..... | ..... | ..... | 0.800 | ..... | ..... | 0.757 | ..... | ..... | 0.775 | ..... | ..... |
| E. T. ..... | −7 | 0.825 | ..... | ..... | 0.769 | ..... | ..... | 0.776 | ..... | ..... | 0.789 | ..... | ..... | 0.768 | ..... | ..... |

* Periods 1, 2, 3 and 4 in the case of protein and fat occurred two, four, six and eight hours after the ingestion of the meal; in the case of carbohydrate one-half, one, two and three hours after ingestion.

† This subject probably ate something before reporting for the experiment.

TABLE 11.—*Pulse Rate and Heat Production* of Obese, Thin and Normal People After the Ingestion of Protein, Carbohydrate and Fat*

| Subject | Percentage of Variation from Normal Weight | Basal | | | | | | 1† | | | | | | 2 | | | | 3 | | | | 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Protein | | Carbohydrate | | Fat | | Protein | | Carbohydrate | | Fat | | Protein | | Carbohydrate | | Fat | | Protein | | Carbohydrate | | Fat | |
| | | Pulse Rate | Calories | Pulse Rate | Calories* | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories | Pulse Rate | Calories |
| | | Overweight | | | | | | | | | | | | | | | | | | | | | | | |
| M. S. | +141 | .. | .... | 70 | 38.1 | .. | .... | .. | .... | 77 | 46.6 | .. | .... | .. | .... | 80 | 42.7 | .. | .... | .. | .... | 78 | 43.6 | .. | .... | .. | .... | 74 | 41.5 | .. | .... |
| | +136 | .. | .... | .. | .... | 76 | 42.4 | .. | .... | .. | .... | 85 | 41.6 | .. | .... | .. | .... | 104 | 44.0 | .. | .... | .. | .... | 80 | 42.0 | .. | .... | .. | .... | 75 | 39.1 |
| E. M. | + 96 | 80 | 41.1 | .. | .... | .. | .... | 94 | 41.9 | .. | .... | .. | .... | 74 | 41.8 | .. | .... | .. | .... | 74 | 39.2 | .. | .... | .. | .... | 74 | 39.7 | .. | .... | .. | .... |
| | + 97 | 75 | .... | .. | .... | .. | .... | 80 | 43.8 | .. | .... | .. | .... | 79 | 43.1 | .. | .... | .. | .... | 77 | 39.9 | .. | .... | .. | .... | 72 | 40.3 | .. | .... | .. | .... |
| | + 96 | .. | .... | 80 | 41.0 | .. | .... | .. | .... | 85 | 50.4 | .. | .... | .. | .... | 87 | 49.3 | .. | .... | .. | .... | 82 | 42.1 | .. | .... | .. | .... | 77 | 39.6 | .. | .... |
| | + 99 | .. | .... | .. | .... | 79 | 42.0 | .. | .... | .. | .... | 75 | 40.4 | .. | .... | .. | .... | 78 | 41.1 | .. | .... | .. | .... | 79 | 40.9 | .. | .... | .. | .... | 74 | 40.2 |
| E. S. | + 91 | 99 | 47.9 | .. | .... | .. | .... | 90 | 45.8 | .. | .... | .. | .... | 80 | 41.6 | .. | .... | .. | .... | 80 | 44.2 | .. | .... | .. | .... | 80 | 43.9 | .. | .... | .. | .... |
| | + 90 | .. | .... | 82 | 43.2 | .. | .... | .. | .... | 80 | 46.5 | .. | .... | .. | .... | .. | .... | .. | .... | .. | .... | 74 | 44.7 | .. | .... | .. | .... | 79 | 41.9 | .. | .... |
| M. N. | + 72 | 77 | 30 | .. | .... | .. | .... | 82 | 24 | .. | .... | .. | .... | 79 | 23 | .. | .... | .. | .... | 80 | 23 | .. | .... | .. | .... | 82 | 32 | .. | .... | .. | .... |
| F. P. | + 64 | 72 | 38.8 | .. | .... | .. | .... | 64 | 36.6 | .. | .... | .. | .... | 68 | 39.1 | .. | .... | .. | .... | 66 | 38.1 | .. | .... | .. | .... | 62 | 41.5 | .. | .... | .. | .... |
| | + 68 | .. | .... | 58 | 33.7 | .. | .... | .. | .... | 70 | 42.5 | .. | .... | .. | .... | 70 | 39.5 | .. | .... | .. | .... | 68 | 37.5 | .. | .... | .. | .... | 86 | 37.2 | .. | .... |
| P. | + 58 | 86 | 33.5 | .. | .... | .. | .... | 75 | 34.2 | .. | .... | .. | .... | 77 | 35.4 | .. | .... | .. | .... | 83 | 34.1 | .. | .... | .. | .... | 84 | 33.3 | .. | .... | .. | .... |
| S. A. | + 56 | 74 | 36.9 | .. | .... | .. | .... | 74 | 42.5 | .. | .... | .. | .... | 73 | 38.9 | .. | .... | .. | .... | 80 | 37.6 | .. | .... | .. | .... | 76 | 35.8 | .. | .... | .. | .... |
| | + 51 | .. | .... | 89 | 41.2 | .. | .... | .. | .... | 90 | 44.8 | .. | .... | .. | .... | 94 | 42.5 | .. | .... | .. | .... | 88 | 41.6 | .. | .... | .. | .... | 88 | 41.5 | .. | .... |
| R. K. | + 45 | 90 | 42 | .. | .... | .. | .... | 85 | 47 | .. | .... | .. | .... | 85 | 43 | .. | .... | .. | .... | 88 | 43 | .. | .... | .. | .... | 88 | 45 | .. | .... | .. | .... |
| | + 43 | 81 | 35.9 | .. | .... | .. | .... | 80 | 39.4 | .. | .... | .. | .... | 84 | 41.5 | .. | .... | .. | .... | 76 | 39.2 | .. | .... | .. | .... | 85 | 37.4 | .. | .... | .. | .... |
| | + 48 | .. | .... | 82 | 46.9 | .. | .... | .. | .... | 81 | 45.2 | .. | .... | .. | .... | 79 | 51.2 | .. | .... | .. | .... | 76 | 44.2 | .. | .... | .. | .... | 78 | 42.2 | .. | .... |
| A. D. | + 37 | .. | 41.1 | .. | .... | .. | .... | 84 | 43.7 | .. | .... | .. | .... | 84 | 46.4 | .. | .... | .. | .... | 74 | 42.9 | .. | .... | .. | .... | 74 | 43.3 | .. | .... | .. | .... |
| | + 33 | .. | .... | 78 | 38.0 | .. | .... | .. | .... | 82 | 41.8 | .. | .... | .. | .... | 78 | 40.5 | .. | .... | .. | .... | 74 | 44.0 | .. | .... | .. | .... | 78 | 38.6 | .. | .... |
| | + 35 | .. | .... | .. | .... | 76 | 36.5 | .. | .... | .. | .... | 76 | 40.8 | .. | .... | .. | .... | 74 | 41.7 | .. | .... | .. | .... | 70 | 39.7 | .. | .... | .. | .... | 70 | 42.2 |
| | + 44 | .. | .... | .. | .... | 74 | 39.4 | .. | .... | .. | .... | 72 | 41.6 | .. | .... | .. | .... | 77 | 42.2 | .. | .... | .. | .... | 76 | 42.2 | .. | .... | .. | .... | 76 | 42.8 |
| Average | | | 38.6 | | 39.4 | | 40.1 | | 39.9 | | 45.4 | | 41.1 | | 39.4 | | 44.3 | | 42.3 | | 38.1 | | 42.5 | | 41.2 | | 39.2 | | 40.4 | | 41.1 |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Underweight** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| E. T. | —11 | .. | .... | 72 | 32 | .. | .... | .. | .... | 82 | 36 | .. | .... | .. | .... | 80 | 37 | .. | .... | .. | .... | 88 | 38 | .. | .... | .. | .... | 66 | 30 | .. | .... |
| | —11 | .. | .... | .. | .... | 68 | 35 | .. | .... | .. | .... | 68 | 37 | .. | .... | .. | .... | 72 | 37 | .. | .... | .. | .... | 72 | 33 | .. | .... | .. | .... | 72 | 37 |
| J. W. | —11 | 64 | 37 | .. | .... | .. | .... | 66 | 41 | .. | .... | .. | .... | 72 | 41 | .. | .... | .. | .... | 64 | 35 | .. | .... | .. | .... | 64 | 32 | .. | .... | .. | .... |
| | —11 | .. | .... | 66 | 33 | .. | .... | .. | .... | 72 | 41 | .. | .... | .. | .... | 72 | 43 | .. | .... | .. | .... | 72 | 39 | .. | .... | .. | .... | 60 | 32 | .. | .... |
| | —10 | .. | .... | .. | .... | 66 | 32 | .. | .... | .. | .... | 72 | 36 | .. | .... | .. | .... | 68 | 37 | .. | .... | .. | .... | 64 | 34 | .. | .... | .. | .... | 60 | 33 |
| H. B. | —14 | 80 | 35 | .. | .... | .. | .... | 76 | 40 | .. | .... | .. | .... | 72 | 40 | .. | .... | .. | .... | 76 | 38 | .. | .... | .. | .... | 68 | 35 | .. | .... | .. | .... |
| | —14 | .. | .... | 74 | 35 | .. | .... | .. | .... | 84 | 37 | .. | .... | .. | .... | 76 | 36 | .. | .... | .. | .... | 76 | 34 | .. | .... | .. | .... | 76 | 32 | .. | .... |
| | —15 | .. | .... | .. | .... | 72 | 34 | .. | .... | .. | .... | 72 | 35 | .. | .... | .. | .... | 84 | 36 | .. | .... | .. | .... | 72 | 35 | .. | .... | .. | .... | 80 | 36 |
| Z. O. | —19 | 77 | 36 | .. | .... | .. | .... | 80 | 41 | .. | .... | .. | .... | 81 | 43 | .. | .... | .. | .... | 84 | 39 | .. | .... | .. | .... | 87 | 38 | .. | .... | .. | .... |
| M. C | —21 | .. | .... | 84 | 38 | .. | .... | .. | .... | 86 | 44 | .. | .... | .. | .... | 96 | 44 | .. | .... | .. | .... | 94 | 45 | .. | .... | .. | .... | 88 | 37 | .. | .... |
| | —20 | .. | .... | .. | .... | .. | 36 | .. | .... | .. | .... | 76 | 39 | .. | .... | .. | .... | 84 | 40 | .. | .... | .. | .... | 88 | 41 | .. | .... | .. | .... | 96 | 43 |
| A. K. | —20 | .. | .... | .. | 35 | .. | .... | .. | .... | .. | 39 | .. | .... | .. | .... | .. | 36 | .. | .... | .. | .... | .. | 40 | .. | .... | .. | .... | .. | 34 | .. | .... |
| M. A. | —22 | 90 | 31 | .. | .... | .. | .... | 84 | 39 | .. | .... | .. | .... | 84 | 38 | .. | .... | .. | .... | 82 | 35 | .. | .... | .. | .... | 85 | 32 | .. | .... | .. | .... |
| | —22 | 86 | 33 | .. | .... | .. | .... | 80 | 36 | .. | .... | .. | .... | 84 | 38 | .. | .... | .. | .... | 84 | 38 | .. | .... | .. | .... | 89 | 35 | .. | .... | .. | .... |
| B. D. | —26 | 81 | 38.2 | .. | .... | .. | .... | 75 | 42.1 | .. | .... | .. | .... | 77 | 42.6 | .. | .... | .. | .... | 78 | 44.8 | .. | .... | .. | .... | 87 | 43.8 | .. | .... | .. | .... |
| | —26 | .. | .... | 77 | 35 | .. | .... | .. | .... | 88 | 41 | .. | .... | .. | .... | 95 | 43 | .. | .... | .. | .... | 96 | 44 | .. | .... | .. | .... | 92 | 43 | .. | .... |
| | —26 | .. | .... | .. | .... | 76 | 35 | .. | .... | .. | .... | 68 | 38 | .. | .... | .. | .... | 68 | 37 | .. | .... | .. | .... | 80 | 41 | .. | .... | .. | .... | 77 | 39 |
| B. M. | —28 | 85 | 36 | .. | .... | .. | .... | 91 | 45 | .. | .... | .. | .... | 89 | 46 | .. | .... | .. | .... | 89 | 40 | .. | .... | .. | .... | 89 | 41 | .. | .... | .. | .... |
| S. S. | —31 | 55 | 35.9 | .. | .... | .. | .... | 62 | 46.3 | .. | .... | .. | .... | 61 | 46.4 | .. | .... | .. | .... | 74 | 41.7 | .. | .... | .. | .... | 64 | 42.0 | .. | .... | .. | .... |
| | —30 | .. | .... | .. | 37 | .. | .... | .. | .... | .. | 41 | .. | .... | .. | .... | .. | 41 | .. | .... | .. | .... | .. | 42 | .. | .... | .. | .... | .. | 41 | .. | .... |
| | —31 | .. | .... | .. | .... | 66 | 38 | .. | .... | .. | .... | 67 | 43 | .. | .... | .. | .... | 73 | 40 | .. | .... | .. | .... | 70 | 40 | .. | .... | .. | .... | 70 | 41 |
| Average.. | | | 35.3 | | 35.0 | | 35.0 | | 41.3 | | 39.9 | | 38 | | 41.9 | | 40 | | 37.8 | | 38.9 | | 40.3 | | 37.7 | | 37.4 | | 35.6 | | 38.2 |
| **Normal** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| M W. | +1 | 71 | 42 | .. | .... | .. | .... | 73 | 49 | .. | .... | .. | .... | 67 | 46 | .. | .... | .. | .... | 66 | 43 | .. | .... | .. | .... | 68 | 44 | .. | .... | .. | .... |
| | —1 | .. | .... | 63 | 39 | .. | .... | .. | .... | 73 | 46 | .. | .... | .. | .... | 76 | 45 | .. | .... | .. | .... | 81 | 44 | .. | .... | .. | .... | 78 | 41 | .. | .... |
| | —2 | .. | .... | .. | .... | 69 | 39 | .. | .... | .. | .... | 68 | 41 | .. | .... | .. | .... | 69 | 40 | .. | .... | .. | .... | 70 | 43 | .. | .... | .. | .... | 64 | 41 |
| D. K. | +0 | 78 | 36 | .. | .... | .. | .... | 84 | 43 | .. | .... | .. | .... | 83 | 44 | .. | .... | .. | .... | 82 | 42 | .. | .... | .. | .... | 82 | 40 | .. | .... | .. | .... |
| | —1 | .. | .... | 74 | 33 | .. | .... | .. | .... | 87 | 43 | .. | .... | .. | .... | 90 | 42 | .. | .... | .. | .... | 86 | 41 | .. | .... | .. | .... | 80 | 36 | .. | .... |
| | +2 | .. | .... | .. | .... | 74 | 35 | .. | .... | .. | .... | 71 | 38 | .. | .... | .. | .... | 80 | 37 | .. | .... | .. | .... | 76 | 37 | .. | .... | .. | .... | 73 | 36 |
| J. S. | +3 | 71 | 37 | .. | .... | .. | .... | 76 | 43 | .. | .... | .. | .... | 78 | 52 | .. | .... | .. | .... | 68 | 41 | .. | .... | .. | .... | 69 | 39 | .. | .... | .. | .... |
| | +3 | .. | .... | 69 | 37 | .. | .... | .. | .... | 80 | 48 | .. | .... | .. | .... | 86 | 46 | .. | .... | .. | .... | 78 | 41 | .. | .... | .. | .... | 71 | 37 | .. | .... |
| | +2 | .. | .... | .. | .... | 56 | 38 | .. | .... | .. | .... | 66 | 41 | .. | .... | .. | .... | 63 | 39 | .. | .... | .. | .... | 61 | 40 | .. | .... | .. | .... | 52 | 36 |
| M. S. | +3 | 63 | 34 | .. | .... | .. | .... | 68 | 41 | .. | .... | .. | .... | 68 | 42 | .. | .... | .. | .... | 66 | 40 | .. | .... | .. | .... | 78 | 39 | .. | .... | .. | .... |
| | +2 | 70 | 36 | .. | .... | .. | .... | 71 | .... | .. | .... | .. | .... | 68 | 43 | .. | .... | .. | .... | 65 | 36 | .. | .... | .. | .... | 65 | 35 | .. | .... | .. | .... |
| E. T. | —7 | 70 | 38 | .. | .... | .. | .... | 74 | 43 | .. | .... | .. | .... | 73 | 40 | .. | .... | .. | .... | 69 | 37 | .. | .... | .. | .... | 74 | 36 | .. | .... | .. | .... |
| Average | | | 37.2 | | 36.3 | | 37.3 | | 43.8 | | 45.7 | | 40 | | 44.5 | | 44.3 | | 38.7 | | 39.8 | | 42.0 | | 40.0 | | 38.8 | | 38.0 | | 37.7 |

* Computed as calories per square meter of body surface per hour.

† Periods 1, 2, 3 and 4 in the case of protein and fat occurred two, four, six and eight hours after the ingestion of the meal; in the case of carbohydrate, one-half, one, two and three hours after ingestion.

overweight and the normal. The average percentage of total calories derived from protein by the obese during the basal period was 17 per cent., followed in the two hour periods by 18, 20, 17 and 16 per cent., respectively; the normals showed 17, 18, 15, 14 and 14 per cent. for the corresponding periods, and the underweights 27, 23, 20, 17 and 12 per cent. Again the underweight people seem to derive more energy from protein.

Table 10 is a record of the respiratory quotients of all subjects in all periods. It was on these figures that the foregoing work was based.

The pulse rate was taken at the end of each metabolism test and is recorded in Table 11. There is no close relation between pulse rate and heat produced per square meter of body surface. Making the comparison on one subject at different times or on different subjects at comparable times, we fail to note any interdependence of these two factors. For instance, M. S. on a carbohydrate meal showed a maximum pulse rate of 80 one hour after the meal, whereas her maximum metabolism, 47 calories per square meter, occurred thirty minutes after the meal while the pulse rate was 77. The same is true with most of the other cases. M. N. showed a drop in metabolism after the high protein meal and a rise in pulse rate. Among the underweights the lowest metabolism occurred in conjunction with the highest basal pulse rate, in M. A.

## SUMMARY

1. The present work is concerned with the energy derived from the various nutrients by obese, normal and thin people after the ingestion of meals high in protein, carbohydrate and fat, respectively. There were twenty-six tests on obese subjects, twenty-one on thin subjects and twelve on normals.

2. After the ingestion of protein, obese people have a tendency to derive their energy from carbohydrate, whereas thin and normal people use less carbohydrate than during starvation. Calories derived from fat decrease in the obese after the meal, but show little change in the thin and normals. The two latter groups, however, show a decided rise in calories derived from protein after the meal, but the protein consumption is little affected in the obese. This confirms our previous finding[2] that there is very little specific dynamic action of protein in obese people.

3. All subjects derive more energy from carbohydrate after the ingestion of a high carbohydrate meal, and less from fat. Calories derived from protein after this meal vary little, however, in any group from the starvation figures.

4. After the high fat meal all groups show an increase in energy derived from fat. The obese continue to use carbohydrate in greater amounts than the two other groups. The protein consumption shows very little change, especially in the obese and normals.

5. There is no relation between the pulse rate and energy production computed on the basis of heat produced per square meter of body surface.

6. The fact that the obese subjects derive less energy from fat than either the thin or the normals after meals indicates a reason for excessive fat storage.

# DISEASES OF THE LIVER

## III. A COMPARATIVE STUDY OF CERTAIN TESTS FOR HEPATIC FUNCTION IN PATIENTS WITH OBSTRUCTIVE JAUNDICE *

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Jaundice is the condition due to the presence of bile pigment in the blood and is recognized clinically by the resultant staining of the skin, conjunctiva, mucous membranes, blood serum and, as a rule, the urine by the bile pigment.

Like albuminuria, jaundice is a symptom and not a disease, and may be encountered in a number of different conditions, the common and essential factor being obstruction to, or failure of, the normal process of excretion of the bile.

A mechanical obstruction to the passage of bile through the larger or extrahepatic bile ducts rapidly leads to resorption of pigments and the development of jaundice. The mechanism of this resorption and the pathway through which the absorbed bile enters the general circulation have been studied by many experimenters from the time of Saunders [1] (1803) to that of Bloom [2] (1923). The experiments of the former served to emphasize the importance of the resorption of the bile pigment through the lymphatic channels and the thoracic duct in the development of jaundice. The latter likewise finds that after ligation of the common bile duct, bile appears in the lymphatic vessels before it can be demonstrated in the blood stream. The obstructive type of jaundice has long been recognized as one of the least complicated forms of icterus. The other varieties of icterus, the so-called hepatogenous and hematogenous forms, will be reviewed in connection with the clinical discussion of toxic or infectious jaundice and the hemolytic anemias.

The clinical symptoms of obstruction to the biliary passages are characteristic and distinct. Icterus; staining of the secretions, especially of the urine with bile pigment; the absence of bile from the stools with

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* From the Division of Medicine, Mayo Clinic and the Mayo Foundation, and the Division of Surgery, Mayo Clinic.

1. Saunders, William: A Treatise on the Structure, Economy and Diseases of the Liver with an Inquiry into the Properties and Competent Parts of Bile and Bibliary Calculi, Ed. 4, London, Phillips, 1809.

2. Bloom, William: The Rôle of the Lymphatics in the Absorption of Bile Pigment from the Liver in Early Obstructive Jaundice, Bull. Johns Hopkins Hosp. **34**:316-320 (Sept.) 1923.

resultant disturbance in fat absorption, producing the characteristic acholic, clay-colored stool; pruritus, and a delay in the coagulation time of the blood with consequent tendency to hemorrhage are constantly present. Bradycardia is less common. Pain, chills, fever and other evidences of infection, such as leukocytosis, are variable. Gastro-intestinal disturbance, with nausea, anorexia and loss in weight and strength, is common; this is also further aggravated by the primary nutritional disturbance consequent on the absence of bile from the intestine. Cerebral symptoms also occur, but these are usually associated with a terminal toxemia and appear late in the sequence of manifestations.

Jaundice due to obstruction of the biliary passages is well tolerated in the main. Cases have been reported with persistent and possibly continuous icterus for years without serious disturbance of the health of the patient apart from the discoloration of the skin and pruritus. Such a condition is in marked contrast to the icterus gravis associated with acute yellow atrophy of the liver, in which the marked disturbance in the activity of the liver results in the rapid development of profound toxemia and death. Although obstructive jaundice is often well borne and recovery usually rapid following relief from the obstruction, a certain proportion of patients do not stand operation and die with symptoms of toxemia somewhat similar to those observed in cases of acute yellow atrophy.

That obstructive jaundice is not without an effect on the liver is evidenced by the production of the pathologic changes characteristic of biliary cirrhosis by bile retention over any extended period. Physiologic disturbances in the activity of the liver, apart from the jaundice, have not been so conclusively shown to accompany these morphologic changes. As we have indicated in the initial paper of this series,[3] this is in part due to the difficulty of obtaining exact criteria and reliable quantitative tests for disturbances in the activity of the liver. We have been able to show disturbances of hepatic function in animals following the experimental ligation of the common bile duct,[4] in which a parallel increase in the serum bilirubin and degree of retention of phenoltetrachlorphthalein was the most striking change noted. We shall present here the results of the study of a series of cases of obstructive jaundice.

The cases may be divided into two groups: the larger comprising forty-three cases of obstructive jaundice, the smaller, twenty-four cases of chronic cholecystitis without clinical evidences of jaundice. The latter

3. Greene, C. H.; Snell, A. M., and Walters, Waltman: Clinical and Experimental Studies in Diseases of the Liver, I, A Survey of Tests for Hepatic Function, Arch. Int. Med., to be published.

4. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Clinical and Experimental Studies in Diseases of the Liver, II, A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med., to be published.

group serves as a control of the effect of cholecystic disease alone. The technic of the laboratory tests and the normal values for each have been reported in the first paper of the series.[3]

## OBSTRUCTIVE JAUNDICE

*Obstructive Jaundice Due to Stone in the Common Bile Duct.*—Cabot [5] reports that the most common types of jaundice are the icterus neonatorum and that which owes its origin to an infection or sepsis. Jaundice due to stone in the common duct is the next in order of frequency. In Table 1 are shown the different laboratory findings in a series of cases of obstructive jaundice due to the impaction of stone in the common bile duct. In each case the diagnosis was verified by the surgeon's findings at operation. The complete history in each case is not essential to this study, but the histories of two illustrative cases are included to show the general nature of the clinical findings.

Only those positive findings on which conclusions are based at the present time are included in the case reports. The phenoltetrachlorphthalein reading is recorded as for the end of the first hour only. Complete findings are included in the tables. Complete details of the surgical procedure are not given, since the patients were regularly prepared according to Walters' [6] method.

## REPORT OF CASES

CASE 1 (Case 12, Table 1).—*Chronic cholecystitis with cholelithiasis, choledocholithiasis and obstructive jaundice.*—A man, aged 59, came to the Mayo Clinic, June 17, 1924, because of jaundice of five weeks' duration. Eighteen months before, he had had an attack of severe pain at the right costal margin which radiated to the shoulder. Five weeks before, he had had a second similar attack, three days after which the stools became acholic, the urine saffron, and persistent jaundice developed. The patient lost 20 pounds (9 kg.) in the five weeks before coming to the clinic. Marked jaundice was present, but the liver was not palpable. The serum bilirubin was 18.2 mg. There was marked retention of phenoltetrachlorphthalein, the reading being 30 per cent. Chronic cholecystitis and cholelithiasis were found, and there was a stone in the ampulla of Vater. There were signs of chronic pancreatitis and chronic hepatitis. The gallbladder and the stones were removed and a drain placed in the common duct. Bile drained freely. Eighteen days after operation, the serum bilirubin had fallen to 6.7 mg. and the phenoltetrachlorphthalein retention to 8 per cent.

CASE 2 (Case 14, Table 1, Fig. 1).—*Chronic cholecystitis with cholelithiasis and obstructive jaundice.*—A man, aged 63, came to the Mayo Clinic, June 16, 1924, complaining of abdominal pain and jaundice of six weeks' duration. For twenty-five years he had had bilious attacks associated with nausea, and pain in the right upper quadrant. He had been definitely jaundiced once, four or five years before. There had been acute attacks recently with severe epigastric pain radiating to the right shoulder, and after the last attack the urine became dark and the stools acholic, accompanied by intense pruritus and jaundice.

5. Cabot, R. C.: Differential Diagnosis, Ed. 2, Philadelphia, W. B. Saunders Company, 1912.

6. Walters, W.: Preoperative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. & Obst. **33**:651 (Dec.) 1921.

The patient lost 35 pounds (15.9 kg.) in the preceding six months. The liver edge was palpable, but the gallbladder was not. Roentgenograms of the gallbladder area showed stones. The serum bilirubin was 16 mg.; the phenoltetrachlorphthalein reading of 28 per cent. indicated marked retention. At operation the liver was found to be hard and congested. The gallbladder contained no bile, but was completely adherent to a large gallstone which compressed the common duct. Cholecystectomy was performed and a drain inserted in the common duct.

Biliary drainage was established but failed progressively, while the jaundice increased and a marked toxemia developed. Four days after operation the patient was critically ill; there was no bile drainage; the serum bilirubin was 16.9 mg. and the blood urea 146 mg. The intravenous administration of 500 c.c. of 20 per cent. glucose solution produced a marked improvement in the general clinical condition. The bile flow was reestablished. Three days later the blood urea was 111 mg. and the serum bilirubin 6.7 mg. Improvement continued

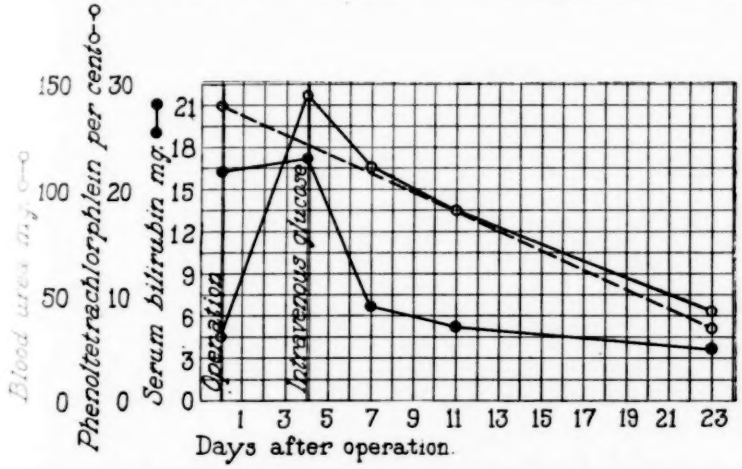


Fig. 1.—Changes in serum bilirubin, phenoltetrachlorphthalein retention and blood urea in Case 2.

and the patient was dismissed about three weeks after the operation. At that time the serum bilirubin was 3.8 mg.; the phenoltetrachlorphthalein retention was 7 per cent., and the blood urea 42 mg.

*Obstructive Jaundice Due to Postoperative Stricture of the Common Duct.*—Present surgical practice is to make cholecystectomy the operation of choice in the majority of cases of gallbladder disease. Injury to the ducts during the removal of the gallbladder is an accident dreaded by every surgeon. Judd and Burden [7] have recently pointed out the factors that predispose to damage. If the injury is recognized immediately, repair usually can be easily and satisfactorily made. When the injury escapes the attention of the surgeon, nature proceeds with repair, but

7. Judd, E. S., and Burden, V. G.: Postoperative Structure of the Common Bile Duct, Ann. Surg. **80**:210-216 (Aug.) 1924.

TABLE 1.—*Obstructive*

| Case | Date | Age, Years | Sex* | Edge of Liver Palpable, Cm. | Jaundice | Duration of Jaundice | Urine: Specific Gravity | Urine: Albumin | Urine: Casts | Urine: Bile Pigments | Blood Count: Hemoglobin, per Cent. | Blood Count: Erythrocytes, Millions | Blood Count: Leukocytes | Phenolsulphonephthalein, per Cent. | Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen | Urea | Uric Acid | Creatinin | Amino-Acid Nitrogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cases with Obstruction of the Common Duct | | | | | | | | | | | | | |
| 1 | 11/ 5/24 | 54 | ♂ | 0 | 3 | 1 wk. | 1.006 | 0 | 0 | + | 75 | 4.65 | 9,800 | .. | 25 | 9 | 3.6 | 1.3 | 6.6 |
| 2 | 10/ 7/24 | 42 | ♀ | 0 | 3 | 2 mo. | 1.008 | 0-1 | 0 | + | 64 | 3.66 | 7,600 | 45 | 21 | 16 | 2.7 | 1.5 | 5.4 |
| 3 | 5/10/24 | 49 | ♀ | 1 | 2 | 10 mo. | 1.031 | 0-1 | 0 | + | 72 | 4.12 | 5,200 | .. | 28 | 25 | 2.3 | 1.4 | 6.2 |
| 4 | 7/17/23 | 45 | ♀ | 5 | 3 | 12 mo. | 1.013 | 0 | 1 | .. | 83 | 4.06 | 10,000 | .. | .. | 27 | 2.8 | 2.0 | ... |
| 5 | 2/13/24 | 69 | ♀ | + | 1 | 2 wk. | 1.016 | 1 | 1-3 | .. | 72 | 4.10 | 5,200 | 45 | 32 | 32 | ... | ... | ... |
| 6 | 5/ 1/24 | 53 | ♀ | Enlarged | 3 | 7 wk. | 1.005 | 0-1 | 1 | + | 68 | 3.82 | 6,400 | 40 | 31 | 31 | 3.3 | 1.2 | 6.1 |
| 7 | 6/ 6/23 | 67 | ♂ | 0 | 2 | Intermittent | 1.022 | 1 | 1 | + | 70 | 4.07 | 6,300 | 60 | 28 | 38 | 0.0 | 1.6 | 4.8 |
| 8 | 9/ 5/23 | 46 | ♀ | + | 3 | 24 mo. | 1.005 | 0-1 | 0 | .. | 63 | 3.70 | 7,600 | 50 | .. | 18 | 2.9 | 1.2 | ... |
| 9 | 1/22/24 | 70 | ♂♀ | + | 4 | 1 wk. | 1.021 | 2 | 1-4 | + | 78 | 4.43 | 7,500 | .. | 37 | 36 | ... | ... | ... |
| 10 | 4/22/24 | 60 | ♂♀ | 4 | 2 | 3 wk. | 1.031 | 1 | 0 | + | 73 | 4.06 | 6,300 | 55 | 29 | 31 | 2.3 | 1.3 | 5.8 |
| 11 | 6/ 5/23 | 56 | ♂ | Enlarged | 2 | 2 mo. | 1.010 | 0 | 0 | .. | 76 | 5.25 | 8,600 | .. | .. | 22 | 3.1 | 1.6 | 7.0 |
| | | | | | | Cases Studied Before and After Relief of Obstruction | | | | | | | | | | | | | |
| 12 | 6/20/24 | 59 | ♂ | 0 | 3 | 1 mo. | 1.001 | 0 | 0 | .. | 68 | 3.80 | 5,400 | .. | 24 | 15 | 0.0 | 1.2 | 5.7 |
| | 7/17/24 | .. | .. | 0 | 1 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | 28 | 28 | 2.2 | 1.8 | 5.3 |
| 13 | 6/ 2/24 | 62 | ♀ | 3 | 4 | 12 mo. | 1.031 | 0-1 | 0 | + | 60 | 3.80 | 6,300 | .. | 31 | 35 | 2.9 | 1.3 | 6.1 |
| | 6/13/24 | .. | .. | 3 | 3 | ..... | 1.017 | 0 | 0 | + | .. | .... | ..... | .. | 30 | 32 | 2.1 | 1.7 | 5.3 |
| 14 | 6/23/24 | 63 | ♂ | 1 | 4 | 5 wk. | 1.012 | 0-1 | 1 | + | 70 | 4.28 | 8,000 | .. | 33 | 30 | 3.4 | 1.6 | 5.0 |
| | 7/17/24 | .. | .. | 1 | 1 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | 47 | 42 | 4.1 | 2.3 | 5.4 |
| 15 | 5/30/24 | 43 | ♂ | 4 | 3 | 2 wk. | 1.027 | 3 | 1 | + | 69 | 3.96 | 9,400 | .. | 34 | .. | 2.9 | 1.8 | 6.1 |
| | 6/17/24 | .. | .. | 4 | 0 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | 39 | 33 | 2.7 | 2.1 | 5.3 |
| 16 | 6/ 3/24 | 59 | ♂ | 0 | 2 | 6 mo. | 1.016 | 0-1 | 0 | + | 68 | 3.85 | 5,000 | .. | 19 | 18 | 1.7 | 1.7 | 5.7 |
| | 6/26/24 | .. | .. | 0 | 1 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | .. | 23 | 2.3 | 1.3 | ... |
| 17 | 10/10/23 | 37 | ♂ | 5 | 0 | ..... | 1.028 | 2 | 1 | 0 | 70 | 4.40 | 10,600 | 50 | .. | 35 | 4.8 | 1.6 | ... |

* In this and the following tables, ♂ indicates male; ♀, female.

TABLE 2.—*Obstructive Jaundice*

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice | Duration of Jaundice | Urine: Specific Gravity | Urine: Albumin | Urine: Casts | Urine: Bile Pigments | Blood Count: Hemoglobin, per Cent. | Blood Count: Erythrocytes, Millions | Blood Count: Leukocytes | Phenolsulphonephthalein, per Cent. | Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen | Urea | Uric Acid | Creatinin | Amino-Acid Nitrogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cases with Obstruction of the Common Duct | | | | | | | | | | | | | |
| 18 | 6/18/24 | 28 | ♂ | Palpable | 4 | 7 mo. | 1.015 | 1-2 | 0 | + | 86 | 4.96 | 10,400 | 80 | 24 | 15 | 1.0 | 1.3 | 5.3 |
| 19 | 9/26/24 | 47 | ♀ | Enlarged | 4 | 6 wk. | 1.023 | 1 | 1 | 3 | 67 | 4.13 | 5,200 | .. | 28 | .. | 2.3 | 1.3 | 5.3 |
| 20 | 7/12/23 | 21 | ♀ | 5 | 3 | 1 mo. | 1.016 | 1 | 0 | .. | 80 | 4.95 | 5,600 | 35 | .. | 20 | 2.1 | 1.3 | ... |
| 21 | 10/17/24 | 31 | ♀ | 0 | 3 | 9 wk. | 1.020 | 1 | 0 | 3 | 74 | 3.83 | 9,200 | 45 | 24 | 19 | 2.6 | 1.3 | 5.8 |
| 22 | 11/ 4/24 | 40 | ♀ | Enlarged | 3 | 36 mo. | 1.022 | 1 | 0 | .. | 27 | 2.78 | 7,200 | .. | 35 | 31 | 2.0 | 1.4 | ... |
| 23 | 3/28/24 | 45 | ♀ | 0 | 3 | 11 mo. | 1.021 | 0-2 | 0 | + | .. | .... | ..... | .. | 26 | 17 | 1.8 | 1.2 | 5.9 |
| 24 | 5/27/24 | 55 | ♂ | 0 | 4 | 18 mo. | 1.018 | 1 | 0 | 2 | 68 | 4.38 | 4,300 | 50 | 27 | 48 | 2.4 | 1.8 | 5.8 |
| 25 | 11/20/24 | 56 | ♂ | 0 | 1 | 18 mo. | 1.011 | 0-1 | 0 | 0 | 72 | 4.43 | 10,100 | .. | 31 | 24 | 3.3 | 1.3 | 6.5 |
| 26 | 3/15/24 | 56 | ♂ | 0 | 2 | 8 mo. | 1.022 | 0 | 1 | .. | 79 | 4.39 | 8,400 | .. | 36 | 30 | 2.4 | 1.6 | 6.8 |
| | | | | | | Cases Studied Before and After Relief of Obstruction | | | | | | | | | | | | | |
| 27 | 3/ 7/24 | 34 | ♂ | 4 | 4 | 2 wk. | 1.025 | 1-2 | 1 | 2 | 63 | 4.16 | 9,400 | 65 | 27 | 20 | .... | ... | ... |
| | 3/15/24 | .. | .. | 4 | 2 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | .. | 29 | .... | ... | ... |
| | 3/27/24 | .. | .. | 4 | 1 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | 34 | 23 | 2.5 | 1.4 | 6.4 |
| 28 | 3/17/24 | 34 | ♂ | 2 | 4 | 6 mo. | 1.021 | 1-2 | 2 | 4 | 64 | 3.89 | 10,000 | 60 | 32 | 12 | 1.7 | 1.4 | 4.7 |
| | 4/ 7/24 | .. | .. | 2 | 2 | ..... | 1.009 | 0-1 | 0 | 1 | .. | .... | ..... | .. | 26 | 12 | 2.9 | 1.1 | 5.7 |
| | 5/27/24 | .. | .. | 1 | 0 | ..... | 1.014 | 0-1 | 0 | 0 | .. | .... | ..... | 65 | 27 | 25 | 3.6 | 1.9 | 6.3 |
| | 10/25/24 | .. | .. | 1 | 2 | 3 mo. | 1.028 | 0-1 | 0 | + | .. | .... | ..... | .. | .. | 26 | 2.7 | 1.5 | ... |
| | 11/17/24 | .. | .. | 1 | 0 | ..... | 1.021 | 0-1 | 0 | 0 | .. | .... | ..... | .. | .. | 26 | 2.8 | 1.6 | ... |
| 29 | 1/14/24 | 39 | ♂ | ++ | 1 | 14 mo. | 1.016 | 0-1 | 0 | .. | 74 | 4.94 | 6,900 | .. | .. | 15 | 1.8 | 1.9 | ... |
| | 1/21/24 | .. | .. | ++ | 0 | ..... | 1.022 | 0 | 0 | .. | .. | .... | ..... | .. | .. | 19 | .... | ... | ... |
| | 3/ 4/24 | .. | .. | ++ | 1 | 1 wk. | 1.015 | 0 | 0 | .. | .. | .... | ..... | .. | 27 | .. | .... | ... | ... |
| | 9/26/24 | .. | .. | ++ | 2 | 6 mo. | 1.021 | 0 | 0 | .. | 74 | 4.81 | 11,100 | .. | 30 | 23 | 1.1 | 1.7 | 6.1 |
| 30 | 6/ 4/23 | 59 | ♂ | 0 | 0 | ..... | 1.018 | 0-1 | 1-2 | .. | 80 | 3.75 | 4,200 | 60 | .. | 23 | 2.5 | 1.4 | 6.7 |
| | 8/ 8/23 | .. | .. | 0 | 0 | ..... | ..... | ... | ... | .. | .. | .... | ..... | .. | .. | 23 | 2.9 | 1.7 | ... |
| 31 | 4/ 5/24 | 49 | ♀ | 0 | 0 | ..... | 1.014 | 0 | 0 | 0 | 70 | 4.08 | 7,600 | .. | 26 | 18 | 2.0 | 0.9 | 5.0 |
| 32 | 3/10/24 | 55 | ♀ | Palpable | 1 | 21 mo. | 1.022 | 0-1 | 0 | 0 | 68 | 3.86 | 9,100 | .. | 27 | 20 | .... | ... | ... |

## *Jaundice Due to Stone*

| Bile Index | Bile Pigments (Serum): Serum Bilirubin, Mg., per Cent. | Bile Pigments (Serum): Van den Bergh Direct Reaction | Coagulation Time: Minutes | Coagulation Time: Seconds | Fructose Tolerance, Blood Sugar, Mg., per Cent.: Normal | 1 Hour | 2 Hours | Change | Phenoltetrachlorphthalein, Dye in Serum, per Cent.: 15 Minutes | 1 Hour | 2 Hours | Dye in Urine, Mg. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cases with Obstruction of the Common Duct** | | | | | | | | | | | | | |
| 85 | **15.6** | + | 7 | 45 | ... | ... | ... | .. | .. | **34** | **26** | **2.2** | Chronic cholecystitis with stones; choledocholithiasis |
| .. | **5.5** | + | 10 | 30 | ... | ... | ... | .. | .. | **30** | **26** | ... | Chronic cholecystitis with stones; choledocholithiasis |
| 36 | **9.0** | + | 9 | 30 | 102 | 122 | 113 | 23 | 23 | **30** | 23 | **1.0** | Chronic cholecystitis; stone in hepatic duct |
| 65 | .... | .. | 5 | 14 | ... | ... | ... | .. | 27 | **25** | 25 | **4.0** | Chronic cholecystitis; choledocholithiasis |
| 30 | **4.4** | + | 8 | 50 | 95 | **138** | 133 | **43** | 30 | **25** | 20 | **1.9** | Choledocholithiasis; pancreatitis |
| 48 | **11.2** | + | 8 | 30 | 94 | 114 | 127 | **33** | 23 | **25** | 20 | **3.6** | Chronic cholecystitis; choledocholithiasis |
| 30 | **10.9** | + | 8 | 0 | 87 | 110 | 121 | **34** | 18 | **24** | 22 | **6.0** | Chronic cholecystitis with stones |
| .. | .... | .. | 9 | 5 | ... | ... | ... | .. | 20 | **20** | 20 | **5.2** | Died; choledocholithiasis; cholecystduodenal fistula |
| 43 | **8.1** | + | 7 | 20 | 110 | **138** | 127 | 28 | 27 | **18** | 15 | **1.5** | Choledocholithiasis; biliary cirrhosis |
| 42 | **6.0** | + | .. | .. | ... | ... | ... | .. | .. | **13** | 8 | **0.5** | Chronic cholecystitis; obstructive jaundice |
| 20 | .... | .. | 5 | 25 | ... | ... | ... | .. | 13 | **12** | 6 | **1.0** | Cholelithiasis; obstructive jaundice |
| **Cases Studied Before and After Relief of Obstruction** | | | | | | | | | | | | | |
| .. | **18.2** | + | 9 | 20 | 110 | 130 | 106 | 20 | 30 | **30** | **30** | **5.8** | Choledocholithiasis; pancreatitis |
| .. | **6.7** | + | .. | .. | 75 | 96 | 78 | 21 | 10 | **8** | 6 | **1.1** | 18 days postoperative |
| 75 | **20.3** | + | .. | .. | 149 | **158** | 177 | 28 | 30 | **30** | 30 | **1.8** | Choledocholithiasis; obesity; diabetes |
| 48 | **7.6** | + | 7 | 20 | 185 | **244** | 219 | **59** | 18 | **22** | 22 | **1.4** | After decrease in jaundice |
| 15 | **16.2** | + | 7 | 0 | 87 | 84 | 87 | —3 | 24 | **28** | 32 | **2.5** | Chronic cholecystitis with stone; obstructive jaundice |
| 21 | **3.8** | + | .. | .. | 97 | **108** | 100 | 11 | 8 | 7 | 3 | 0.6 | 3 weeks postoperative |
| .. | **18.3** | + | 8 | 45 | 100 | **140** | 115 | 40 | 23 | **28** | 24 | 0.6 | Chronic cholecystitis with stones; choledocholithiasis |
| .. | **2.1** | + | .. | .. | 117 | .... | 100 | —17 | .. | .. | 2 | 0.2 | 15 days postoperative |
| .. | **13.4** | + | 13 | 0 | 87 | 117 | 91 | **30** | 18 | **22** | 9 | 0.7 | Choledocholithiasis; cholecystoduodenal fistula |
| 13 | **2.5** | + | .. | .. | 96 | 104 | 95 | 8 | 16 | **6** | 4 | 0.5 | 21 days postoperative |
| .. | .... | .. | 6 | 30 | ... | ... | ... | .. | 25 | **20** | 18 | 0.5 | Choledocholithiasis; biliary cirrhosis 3 months after relief of obstruction |

## *Due to Postoperative Stricture*

| Bile Index | Bile Pigments (Serum): Serum Bilirubin, Mg., per Cent. | Bile Pigments (Serum): Van den Bergh Direct Reaction | Coagulation Time: Minutes | Coagulation Time: Seconds | Fructose Tolerance, Blood Sugar, Mg., per Cent.: Normal | 1 Hour | 2 Hours | Change | Phenoltetrachlorphthalein, Dye in Serum, per Cent.: 15 Minutes | 1 Hour | 2 Hours | Dye in Urine, Mg. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cases with Obstruction of the Common Duct** | | | | | | | | | | | | | |
| 366 | **52.7** | + | .. | .. | 100 | 92 | 99 | —8 | 30 | **44** | 34 | **8.8** | Died; postoperative stricture of common duct; biliary cirrhosis |
| .. | **21.1** | + | 9 | 30 | ... | ... | ... | .. | .. | **36** | 30 | **7.2** | Postoperative stricture of common duct |
| .. | .... | .. | .. | .. | 91 | ... | ... | .. | .. | **30** | 27 | **8.2** | Postoperative stricture of common duct |
| 50 | **10.3** | + | 8 | 30 | ... | ... | ... | .. | .. | **26** | 26 | **4.8** | Postoperative stricture of common duct |
| 55 | **8.8** | + | 11 | 0 | ... | ... | ... | .. | .. | **26** | 26 | **5.8** | Postoperative stricture of common duct |
| 34 | **7.6** | + | .. | .. | 100 | 123 | 110 | 23 | .. | **26** | 24 | **1.7** | Postoperative stricture of comomn duct |
| 210 | **32.5** | + | 10 | 30 | 83 | 107 | 87 | 24 | 25 | **25** | 25 | **7.8** | Postoperative stricture of common duct |
| .. | **2.9** | + | 8 | 0 | ... | ... | ... | .. | 14 | **22** | 14 | ... | Postoperative stricture of common duct with intermittent jaundice |
| 14 | **3.2** | + | .. | .. | 113 | 130 | 120 | 17 | 22 | **20** | 17 | **1.3** | Postoperative stricture of common duct with intermittent jaundice |
| **Cases Studied Before and After Relief of Obstruction** | | | | | | | | | | | | | |
| 77 | **18.7** | + | 12 | 25 | 120 | 123 | 125 | 5 | 30 | **48** | 44 | **5.3** | Postoperative stricture of common duct |
| 71 | **17.2** | + | .. | .. | ... | ... | ... | .. | 24 | **24** | 22 | ... | Obstructive jaundice 5 days postoperative |
| 82 | **8.7** | + | .. | .. | 85 | 90 | 81 | 5 | 25 | **28** | 23 | **3.7** | 17 days postoperative |
| 95 | **24.8** | + | 19 | 15 | 85 | 105 | 90 | 20 | 30 | **30** | 30 | **7.0** | Postoperative stricture of common duct |
| 36 | **5.3** | + | 7 | 50 | ... | ... | ... | .. | 9 | 7 | 4 | **1.2** | Obstructive jaundice 12 days postoperative |
| 25 | **2.5** | + | 7 | 20 | 95 | 120 | 98 | 25 | 10 | **10** | 5 | 0.9 | 65 days postoperative |
| 33 | **6.3** | + | .. | .. | 88 | 100 | 95 | 12 | 15 | **15** | 17 | 0.6 | Recurring stricture with obstruction |
| .. | **3.4** | + | .. | .. | 91 | ... | ... | .. | .. | **9** | .. | **1.5** | 15 days postoperative |
| .. | .... | .. | 6 | 30 | 95 | 118 | 92 | 23 | 7 | 3 | 0 | 0.3 | Postoperative stricture of common duct; residual jaundice only |
| .. | .... | .. | 10 | 35 | ... | ... | ... | .. | 2 | 1 | 0 | 0.0 | No jaundice 1 week later |
| 16 | **3.3** | ± | 9 | 25 | ... | ... | ... | .. | 8 | **11** | 8 | ... | Slight jaundice of 1 week's duration |
| .. | **7.6** | + | .. | .. | 98 | 104 | 94 | 6 | 26 | **25** | 25 | **2.5** | Postoperative stricture with nearly complete obstruction |
| .. | .... | .. | .. | .. | ... | ... | ... | .. | 11 | **10** | 8 | 0.2 | Postoperative stricture; biliary fistula with partial obstruction |
| .. | .... | .. | .. | .. | ... | ... | ... | .. | 2 | 1 | 0 | 0.3 | After complete drainage |
| 7 | **2.5** | + | 9 | 25 | 85 | 123 | 100 | **38** | 15 | **17** | 12 | ... | Postoperative stricture of common duct; complete biliary fistula 5 months |
| 8 | 1.5 | + | 13 | 0 | 91 | 111 | 123 | **32** | 8 | 7 | 3 | 0.5 | Postoperative stricture of common duct; partial slight jaundice |

the handicap may be too great and stricture is then prone to follow. Postoperative stricture of the common duct is usually the result of operative trauma, but it may also follow localized infection or necrosis of the wall of the duct. Table 2 shows the laboratory findings in a series of cases of obstructive jaundice originating in this way. The histories of two illustrative cases are also reported in abstract. This report deals with selected cases and the numbers reported in each group should not be interpreted as representing the relative frequency of occurrence of the condition.

CASE 3 (Case 28, Table 2.)—*Postoperative stricture of the common duct with obstructive jaundice.*—A man, aged 34, came to the Mayo Clinic, March 8, 1924. He had been ill since 1912, and several operations had been performed

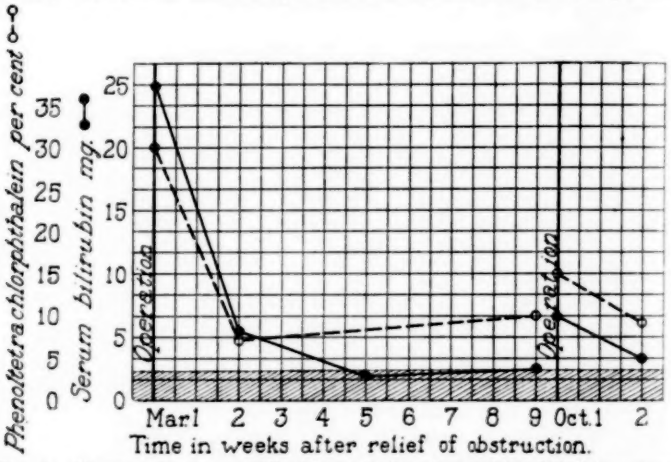


Fig. 2.—Changes in serum bilirubin and phenoltetrachlorphthalein retention in Case 3. The shaded area indicates the range of the normal values of the two tests. The effects of the relief of the obstruction and of a second postoperative stricture are well shown.

elsewhere without permanent relief. In December, 1922, he began to have intermittent attacks of pain at the right costal margin, radiating to the right shoulder. In March, 1923, the gallbladder was removed. Jaundice appeared the following day, although there was free drainage of bile, but recovery was apparently complete after six or seven weeks. In September he developed persistent jaundice without pain. On admission eight months later, the jaundice was marked. The patient had lost 27 pounds (12.2 kg.) during the preceding year. The liver was palpable; the urine contained a trace of albumin and a few granular casts, as well as much bile. The serum bilirubin was 24.8 mg. and there was marked retention of phenoltetrachlorphthalein, as indicated by a reading of 30 per cent.

Operation revealed extensive adhesions and obstruction of the common bile duct due to a stricture. Drainage was established, and the reconstruction of the common duct attempted. The postoperative progress was good. Twelve days after the operation, the serum bilirubin was 5.3 mg., while the phenoltetrachlorphthalein showed slight retention with a reading of 7 per cent. The patient was dismissed April 27, 1924, at which time the serum bilirubin was 2.5 mg. and the phenoltetrachlorphthalein was 10 per cent.

The patient again became ill June 18, 1924, and jaundice reappeared. It varied in intensity, but was associated at times with pruritus, chills, diarrhea and loss of weight. The patient was readmitted October 25, when the condition was similar to that noted on his first admission. Serum bilirubin was 6.3 mg. and the retention of phenoltetrachlorphthalein was 15 per cent. At operation it was found that the hepatic duct was distorted and obstructed by adhesions. A hepaticoduodenostomy over a rubber tube was made. The operation was difficult, but the postoperative recovery was uneventful. Fifteen days after the operation the jaundice had disappeared, and the serum bilirubin was 3.4 mg. while the dye showed 9 per cent. retention. The patient was dismissed a week later.

This case is of particular interest in that it was possible to follow the changes over an extended period. During this time a second stricture developed so that the studies comprise the whole cycle of changes associated with such obstruction.

Case 4 (Case 29, Table 2).—*Recurring postoperative stricture of the common duct with obstructive jaundice.*—A man, aged 39, was admitted to the Mayo Clinic, Jan. 14, 1924, complaining of intermittent jaundice during the last two years, initiated by an attack of acute illness with severe pain in the right upper quadrant. A cholecystectomy was performed at the time of the original attack, but drainage of bile persisted for four months. The last attack began in December, 1923, and continued until the time of admission. The patient lost 17 pounds (7.7 kg.) during the year. The liver was markedly enlarged, but the jaundice was slight and rapidly disappeared. There was slight retention of phenoltetrachlorphthalein; with the complete disappearance of the jaundice the reading decreased from 3 to 1 per cent. At operation many dense adhesions were found, and the common duct contained stones and gravel. Bile flowed freely from the hepatic duct, and hepaticoduodenostomy was performed. The patient did well for a month, when he had a chill followed by slight jaundice. These attacks recurred and he was readmitted March 4, one week after the last attack. At this time jaundice was slight. The serum bilirubin was 3.3 mg. and the phenoltetrachlorphthalein retention was 11 per cent. Duodenal drainage established a good flow of bile. Progress was satisfactory for a short time, but the attacks of chills, fever and jaundice recurred. The patient was again admitted to the clinic September 27, with marked jaundice. The serum bilirubin was 7.6 mg. and the phenoltetrachlorphthalein showed retention of 25 per cent. A marked contraction at the opening of the former anastomosis had occurred; this was successfully relieved.

*Obstructive Jaundice Due to a Tumor of the Head of the Pancreas.*—Next to stones, pressure on the common duct by an enlargement of the head of the pancreas is perhaps the most common cause of obstructive jaundice. Table 3 includes a group of cases in which the jaundice was consequent on obstruction by swelling in the head of the pancreas. In all cases the tumor demonstrable at operation was presumably carcinomatous in nature. Removal of specimens for diagnosis in such cases is not always feasible, and the macroscopic differentiation of chronic pancreatitis and malignant disease is difficult. In each case, however, the obstruction to the bile duct and the resultant jaundice were the outstanding clinical features. Cases of jaundice with proved carcinomatous involvement of the liver will be reported later.

TABLE 3.—*Obstructive Jaundice Due*

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice | Duration of Jaundice | Urine: Specific Gravity | Urine: Albumin | Urine: Casts | Urine: Bile Pigments | Blood Count: Hemoglobin, per Cent. | Blood Count: Erythrocytes, Millions | Blood Count: Leukocytes | Phenolsulphonephthalein, per Cent. | Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen | Urea | Uric Acid | Creatinin | Amino-Acid Nitrogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cases with Obstruction of the Common Duct | | | | | | | | | | | | | |
| 33 | 6/25/24 | 62 | ♂ | 5 | 3 | 1 mo. | 1.021 | 0-1 | 0 | + | 70 | 4.04 | 6,600 | 55 | 30 | 40 | 2.9 | 1.3 | 5.0 |
| 34 | 3/15/24 | 73 | ♀ | Enlarged | 4 | 2 mo. | 1.016 | 2 | 0 | 3 | 70 | 4.21 | 6,100 | 46 | 41 | 20 | 3.7 | 1.7 | ... |
| 35 | 4/18/24 | 52 | ♂ | Enlarged | 4 | 6 da. | 1.016 | 2 | 2 | 2 | 65 | 3.76 | 5,200 | 45 | 33 | 39 | 2.6 | 1.2 | ... |
| 36 | 8/ 1/23 | 34 | ♀ | 1 | 2 | 1 mo. | 1.029 | 1 | 1 | .. | 93 | 4.30 | 11,600 | 60 | .. | 22 | ... | ... | ... |
| 37 | 6/ 5/24 | 56 | ♂ | 1 | 3 | 16 mo. | 1.024 | 4 | 1 | 2 | 75 | 4.18 | 8,700 | 40 | 30 | 26 | 2.2 | 1.7 | 5.1 |
| 38 | 12/11/24 | 55 | ♂ | 3 | 3 | 3 mo. | 1.020 | 1 | 1 | 3 | 65 | 4.20 | 9,100 | 65 | 26 | 16 | 1.7 | 1.1 | ... |
| 39 | 8/ 7/23 | 57 | ♂ | Enlarged | 3 | 1 mo. | 1.003 | 1 | 0 | 2 | 73 | 4.26 | 7,200 | .. | .. | 149 | 6.2 | ... | ... |
| | | | | | | Cases Studied Before and After Relief of Obstruction | | | | | | | | | | | | | |
| 40 | 4/17/24 | 57 | ♂ | Palpable | 0 | ..... | 1.026 | 0 | 0 | 0 | 65 | 3.83 | 5,500 | .. | 29 | 38 | 2.9 | 1.5 | 6.4 |
| | 5/21/24 | .. | .. | Palpable | 4 | 4 wk. | 1.015 | 0-1 | 0 | + | 55 | 3.30 | 6,000 | .. | 34 | 41 | 1.6 | 1.4 | 6.2 |
| 41 | 5/28/24 | 52 | ♂ | Enlarged | 4 | 6 wk. | 1.020 | 2 | 0 | + | 55 | 3.14 | 7,300 | .. | 23 | 38 | 2.1 | 1.4 | 4.6 |
| | 7/19/24 | .. | .. | .. | 0 | ..... | 1.024 | 1 | 0 | 0 | 73 | .... | 8,200 | .. | 27 | 29 | 3.0 | 1.9 | 5.6 |
| 42 | 8/ 2/23 | 52 | ♂ | Enlarged | 4 | 7 wk. | 1.012 | 2 | 1 | .. | 70 | 3.54 | 11,400 | .. | .. | 36 | ... | ... | ... |
| | 2/ 9/24 | .. | .. | .. | 1 | ..... | 1.023 | 0 | 1 | .. | .. | .... | 7,700 | .. | 40 | 37 | 3.0 | 1.9 | ... |
| 43 | 10/27/24 | 44 | ♂ | 0 | 1 | ..... | 1.025 | 0 | 0 | .. | 72 | 4.39 | 7,900 | .. | 37 | 36 | 2.7 | 1.6 | 7.8 |
| | 11/ 8/24 | .. | .. | 0 | 0 | ..... | 1.007 | 0 | 0 | .. | .. | .... | ..... | .. | .. | 22 | 3.0 | 1.5 | ... |

TABLE 4.—*Chronic Cholecystitis*

| Case | Date | Age, Years | Sex | Edge of Liver Palpable, Cm. | Jaundice | Duration of Jaundice | Urine: Specific Gravity | Urine: Albumin | Urine: Casts | Urine: Bile Pigments | Blood Count: Hemoglobin, per Cent. | Blood Count: Erythrocytes, Millions | Blood Count: Leukocytes | Phenolsulphonephthalein, per Cent. | Blood Nitrogen Partition, Mg., per Cent.: Nonprotein Nitrogen | Urea | Uric Acid | Creatinin | Amino-Acid Nitrogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 44 | 5/22/23 | 43 | ♀ | 10 | 0 | * | 1.027 | 0-1 | ... | + | 56 | 5.20 | 12,500 | .. | .. | .. | ... | ... | 7.8 |
| 45 | 12/ 7/23 | 57 | ♂ | 0 | 0 | * | 1.020 | 1 | 1 | .. | 85 | 5.10 | 9,800 | 44 | .. | 24 | ... | ... | ... |
| 46 | 7/ 4/24 | 32 | ♀ | 0 | 0 | 0 | 1.028 | 0 | 0 | 0 | 73 | 4.17 | 5,900 | .. | 43 | 55 | 2.3 | 1.8 | 5.6 |
| | 7/ 8/24 | .. | .. | 0 | 0 | 0 | 1.023 | 0-1 | 0 | 0 | .. | .... | ..... | .. | 34 | 43 | 2.1 | 1.8 | 6.9 |
| 47 | 10/16/24 | 38 | ♀ | 0 | 0 | 0 | 1.012 | 0-1 | 0 | .. | 55 | 3.11 | 9,000 | 80 | 21 | 15 | 1.7 | 1.3 | 4.8 |
| 48 | 10/ 6/23 | 73 | ♀ | 0 | 0 | * | ..... | ... | ... | .. | .. | .... | ..... | .. | .. | 24 | 2.3 | 1.5 | ... |
| 49 | 6/ 4/24 | 47 | ♀ | 0 | 0 | 0 | 1.008 | 0-1 | 0 | .. | .. | .... | 5,400 | .. | 29 | 37 | 0.0 | 1.5 | 6.7 |
| 50 | 11/24/24 | 46 | ♀ | 0 | 0 | 0 | 1.033 | 0 | 0 | .. | 75 | 4.96 | 8,000 | .. | 25 | 25 | 1.9 | 1.2 | 6.2 |
| 51 | 7/ 6/23 | 43 | ♀ | 0 | 0 | * | 1.022 | 0-1 | ... | 0 | 71 | 4.20 | 6,500 | .. | .. | 22 | 2.8 | 2.0 | ... |
| 52 | 5/28/24 | 51 | ♀ | 0 | 0 | 0 | 1.024 | 0 | 0 | .. | 78 | .... | 5,300 | 50 | 30 | 34 | 2.3 | 1.7 | 7.0 |
| 53 | 5/24/24 | 59 | ♀ | 0 | 0 | 0 | 1.031 | 0-1 | 0 | .. | 79 | 4.63 | 8,700 | 55 | 26 | 36 | 2.1 | 1.2 | 6.4 |
| 54 | 9/17/23 | 53 | ♀ | 1 | 0 | 0 | 1.009 | 0 | ... | .. | 75 | .... | 7,400 | .. | .. | 20 | ... | 1.9 | ... |
| 55 | 6/10/24 | 60 | ♀ | 0 | 0 | 0 | 1.022 | 0 | 0 | .. | 70 | 4.23 | 7,600 | 70 | 34 | 46 | 1.7 | 1.3 | 6.9 |
| 56 | 2/12/24 | 44 | ♀ | 0 | 0 | 0 | 1.019 | 0-1 | ... | .. | .. | .... | ..... | 60 | 31 | 19 | ... | ... | ... |
| 57 | 4/24/24 | 49 | ♀ | 1 | 0 | * | 1.009 | 0-1 | 0 | .. | 72 | 4.38 | 10,100 | 75 | 27 | 9 | 2.6 | 1.4 | 6.0 |
| 58 | 7/28/24 | 56 | ♀ | 0 | 0 | 0 | 1.014 | 0 | 0 | .. | 72 | 4.46 | 8,100 | 50 | 31 | 36 | 2.5 | 1.5 | 6.4 |
| 59 | 6/ 9/24 | 34 | ♀ | 0 | 0 | * | 1.024 | 0-1 | 0 | 0 | 64 | 3.26 | ..... | 60 | 35 | 43 | 2.6 | 1.5 | 5.8 |
| 60 | 1/23/24 | 36 | ♀ | 3 | 0 | * | ..... | ... | ... | .. | .. | .... | ..... | .. | 32 | 13 | ... | ... | ... |
| 61 | 1/21/24 | 50 | ♀ | 0 | 0 | 0 | 1.021 | 0 | 1 | .. | 80 | 4.30 | 9,000 | 60 | 33 | 35 | ... | ... | ... |
| 62 | 7/23/23 | 46 | ♀ | 0 | 0 | 0 | 1.008 | 0 | ... | .. | 79 | .... | 12,900 | .. | .. | 27 | 4.0 | 2.0 | ... |
| 63 | 2/ 1/24 | 39 | ♀ | 1 | 0 | * | 1.034 | 1 | ... | .. | 78 | 4.31 | 8,400 | .. | 32 | 32 | ... | ... | ... |
| 64 | 5/29/24 | 41 | ♀ | 0 | 0 | 0 | 1.030 | 0-1 | 0 | .. | .. | .... | ..... | .. | 30 | 26 | 1.8 | 1.7 | 5.4 |
| 65 | 10/10/23 | 43 | ♂ | 0 | 0 | 0 | 1.018 | 0 | ... | .. | 75 | 3.86 | 7,500 | 50 | .. | 26 | ... | ... | ... |
| 66 | 1/ 5/24 | 44 | ♂ | 0 | 0 | 0 | 1.010 | 0 | ... | .. | 78 | 4.64 | 6,700 | 55 | 25 | 17 | ... | ... | ... |
| 67 | 7/10/24 | 47 | ♀ | 1 | 0 | 0 | 1.034 | 0-1 | 0 | 0 | 74 | 4.10 | 6,600 | 65 | 26 | 25 | 2.3 | 1.1 | 7.0 |

* Occasional attacks of jaundice.

| Bile Index | Bile Pigments (Serum): Serum Bilirubin, Mg., per Cent. | Bile Pigments (Serum): Van den Bergh Direct Reaction | Coagulation Time: Minutes | Coagulation Time: Seconds | Fructose Tolerance, Blood Sugar, Mg., per Cent.: Normal | 1 Hour | 2 Hours | Change | Phenoltetrachlorphthalein: Dye in Serum, per Cent.: 15 Minutes | 1 Hour | 2 Hours | Dye in Urine, Mg. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cases with Obstruction of the Common Duct** | | | | | | | | | | | | | |
| 128 | 27.8 | + | .. | .. | 112 | 135 | 127 | 23 | 40 | 44 | 34 | ... | Died; carcinoma of head of pancreas; obstructive jaundice |
| 46 | 24.1 | + | 10 | 45 | 100 | ... | ... | .. | .. | 36 | 28 | ... | Died; tumor at head of pancreas; obstructive jaundice |
| 30 | 35.7 | + | 4 | 30 | ... | ... | ... | .. | 34 | 33 | 30 | ... | Died; tumor at head of pancreas; obstructive jaundice |
| .. | .... | .. | 9 | 40 | ... | ... | ... | .. | 30 | 30 | 30 | 4.2 | Died; carcinoma of papilla of Vater; obstructive jaundice |
| 41 | 8.2 | + | .. | . | ... | ... | ... | .. | 25 | 28 | 25 | 3.0 | Tumor at head of pancreas; obstructive jaundice |
| .. | 15.0 | + | .. | .. | ... | ... | ... | .. | .. | 24 | 20 | ... | Died; carcinoma of head of pancreas; obstructive jaundice |
| .. | .... | .. | 7 | 20 | 95 | 143 | 132 | 48 | .. | 12 | 3 | 0.0 | Died; carcinoma of pancreas; obstructive jaundice |
| **Cases Studied Before and After Relief of Obstruction** | | | | | | | | | | | | | |
| 19 | 3.5 | ± | 6 | 50 | 170 | ... | ... | .. | 7 | 4 | 0 | 0.4 | Died; carcinoma of head of pancreas; before obstruction |
| 143 | 35.6 | + | 13 | 15 | 162 | 197 | 201 | 39 | 24 | 24 | 20 | 4.2 | After obstruction |
| 198 | 14.2 | + | 11 | .. | 85 | 88 | 66 | 3 | 30 | 30 | 30 | 1.0 | Carcinoma of head of pancreas; obstructive jaundice |
| 18 | 1.9 | + | 8 | .. | 85 | 104 | 90 | 19 | .. | .. | .. | ... | Six weeks postoperative |
| .. | .... | .. | .. | .. | 90 | 150 | 177 | 87 | .. | 20 | 20 | 4.5 | Carcinoma of head of pancreas; obstructive jaundice |
| 10 | 1.7 | + | 8 | 25 | 93 | 113 | 92 | 20 | 7 | 9 | 8 | 1.5 | After biliary fistula and drainage |
| 25 | 3.0 | + | .. | .. | ... | ... | ... | .. | 12 | 12 | 7 | 0.5 | Carcinoma of papilla of Vater; obstructive jaundice |
| .. | .... | .. | .. | .. | 100 | ... | ... | .. | 12 | 8 | .. | 1.0 | Twenty days postoperative; thirty-two days postoperative |

*Without Jaundice*

| Bile Index | Bile Pigments (Serum): Serum Bilirubin, Mg., per Cent. | Bile Pigments (Serum): Van den Bergh Direct Reaction | Coagulation Time: Minutes | Coagulation Time: Seconds | Fructose Tolerance, Blood Sugar, Mg., per Cent.: Normal | 1 Hour | 2 Hours | Change | Phenoltetrachlorphthalein: Dye in Serum, per Cent.: 15 Minutes | 1 Hour | 2 Hours | Dye in Urine, Mg. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | .... | .. | .. | .. | ... | ... | ... | .. | 12 | 8 | 2 | ... | Chronic cholecystitis; chronic cholangeitis and hepatitis |
| .. | 1.1 | 0 | 5 | 40 | 123 | 163 | 160 | 40 | 12 | 7 | 3 | 0.3 | Cholelithiasis; pancreatitis |
| 7 | 1.4 | 0 | .. | .. | 90 | 114 | 105 | 24 | 10 | 9 | 5 | 0.4 | Chronic cholecystitis |
| 8 | 1.3 | 0 | .. | .. | 74 | 114 | 90 | 39 | 8 | 5 | 2 | 1.3 | |
| 9 | 0.8 | ± | .. | .. | ... | ... | ... | .. | 10 | 6 | 2 | 0.6 | Chronic cholecystitis with stones |
| .. | .... | .. | 9 | 10 | 85 | 174 | 122 | 89 | 8 | 5 | 4 | 0.3 | Chronic cholecystitis; cholelithiasis |
| .. | 1.5 | 0 | .. | .. | ... | ... | ... | .. | 8 | 6 | 0 | 0.0 | Former cholecystectomy; hepatitis |
| .. | 0.4 | 0 | 9 | .. | ... | ... | ... | .. | .. | 5 | 0 | 0.1 | Former cholecystectomy; cholelithiasis |
| .. | .... | .. | 6 | 10 | ... | ... | ... | .. | 8 | 4 | 0 | 0.8 | Cholelithiasis; intermittent jaundice |
| 8 | 1.4 | 0 | .. | .. | 107 | 115 | 96 | 8 | 10 | 4 | 1 | 0.0 | Chronic cholecystitis |
| 8 | 1.6 | 0 | .. | .. | 86 | 97 | 92 | 11 | 8 | 4 | 2 | 0.3 | Former cholecystectomy; chronic constipation |
| .. | .... | .. | .. | .. | ... | ... | ... | .. | 8 | 4 | 0 | 0.0 | Chronic cholecystitis; chronic appendicitis |
| 6 | 1.1 | 0 | .. | .. | 71 | 87 | 80 | 16 | 6 | 4 | 0 | 0.0 | Former cholecystectomy; cholelithiasis |
| 5 | 1.5 | 0 | .. | .. | 100 | 148 | 127 | 48 | 10 | 3 | 0 | 0.4 | Chronic cholecystitis; hepatitis; diabetes |
| 5 | 0.9 | 0 | .. | .. | 98 | 107 | 92 | 9 | 8 | 3 | 0 | 0.0 | Chronic cholecystitis; hepatitis |
| 6 | 0.4 | 0 | 6 | 15 | 94 | 100 | 97 | 6 | 7 | 3 | 0 | 0.5 | Chronic cholecystitis; hepatitis; pancreatitis |
| 18 | 4.5 | 0 | 9 | 10 | 86 | 95 | 95 | 9 | 6 | 3 | 2 | 0.2 | Chronic cholecystitis 48 hours after an acute attack |
| 8 | 0.6 | 0 | .. | .. | 93 | 105 | 85 | 12 | 5 | 2 | 0 | 0.0 | Chronic cholecystitis |
| .. | 1.8 | 0 | .. | .. | 85 | 127 | 108 | 42 | .. | 2 | 0 | 0.4 | Chronic cholecystitis |
| .. | .... | .. | .. | .. | ... | ... | ... | .. | 7 | 1 | 0 | 0.4 | Former cholecystectomy; postinfluenzal exhaustion |
| 5 | 2.0 | 0 | .. | .. | 86 | 83 | 88 | 2 | 6 | 1 | 0 | 0.2 | Former cholecystectomy; hepatitis |
| 4 | 0.9 | 0 | .. | . | 87 | 117 | 97 | 30 | 6 | 1 | 0 | 0.1 | Former cholecystectomy; pancreatitis; chronic arthritis |
| .. | .... | .. | .. | .. | 160 | 133 | 110 | −50 | 4 | 1 | 0 | 0.2 | Former cholecystectomy; chronic nervous exhaustion |
| .. | 0.0 | 0 | .. | .. | 170 | ... | ... | .. | 4 | 1 | 0 | ... | Chronic cholecystitis; hepatitis; diabetes |
| .. | 0.8 | 0 | 9 | 50 | 97 | 120 | ... | 23 | 3 | 1 | 0 | 0.9 | Chronic cholecystitis; cholelithiasis |

CASE 5 (Case 40, Table 3).—*Obstructive jaundice; tumor of the head of the pancreas.*—A man, aged 57, was first admitted to the Mayo Clinic Nov. 2, 1923, because of pain in the right lumbar region of one week's duration. He had had occasional slight backache for several years and irregular epigastric pain one or two hours after eating for fifteen years. He had been losing weight, especially recently, and the right lumbar pain had become more severe. Physical signs and roentgenograms pointed to pleurisy at the right base. No other definite lesion was discovered, but after the patient's dismissal, the pain in the right upper quadrant and right lumbar region became quite severe. During these attacks the skin developed a subicteric tinge, though there was no definite jaundice. Urobilin and urobilinogen were present in the urine during the crises. Glycosuria and hyperglycemia were sometimes present.

On readmission, April 7, 1924, there was slight tenderness in the right upper quadrant, and an indefinite mass was palpated. Sugar, urobilin and urobilinogen were found in the urine. The serum bilirubin was 3.5 mg.; the phenoltetrachlorphthalein reading was 4 per cent. The patient refused exploratory operation.

Jaundice and pruritus developed after the patient's dismissal from the clinic, and he returned May 18. He had lost 21 pounds (9.5 kg.) in the preceding four weeks. Jaundice 4 was present. The liver was palpable and the epigastric mass could still be felt. The urine contained bile and a trace of albumin. The serum bilirubin was 35.6 mg. and there was marked retention of the phenoltetrachlorphthalein, the reading being 24 per cent. At operation an enlarged soft tumor in the head of the pancreas was found and the gallbladder was greatly distended with bile. There were no stones, and the obstruction was evidently due to the tumor in the head of the pancreas. A cholecystgastrostomy was performed, but the patient died on the third day of bronchopneumonia. Necropsy was not permitted.

The similarity between the changes in the laboratory findings in this patient and those seen in dogs following the experimental ligation of the common bile duct is worthy of especial note.

CASE 6 (Case 33, Table 3).—*Obstructive jaundice; carcinoma of the head of the pancreas.*—A man, aged 62, came to the Mayo Clinic May 13, 1924, having suffered for five months from attacks of epigastric pain, which had begun with a sharp attack the previous January. He had lost 30 pounds (13.6 kg.) since the onset, although there was no jaundice. The liver was palpable and a distended gallbladder could be felt below its margin. The urine contained albumin and pus cells. He had a sudden attack of sharp pain in the right upper quadrant during the examination. Three days later marked persistent jaundice developed. June 24, the serum bilirubin was 27.8 mg. and there was marked retention of phenoltetrachlorphthalein, the reading being 44 per cent. The fructose tolerance test was questionable. At operation a diffuse carcinoma at the head of the pancreas was found to be obstructing the common bile duct. The gallbladder was distended with a great quantity of very thick black bile. The postoperative progress was not satisfactory. The blood urea increased to 91 mg. on the fourteenth day, and the patient died July 17.

### CHRONIC CHOLECYSTITIS WITHOUT JAUNDICE

Many patients with obstructive jaundice have had long standing cholecystic disease apart from the obstruction. The effect of this condition in relation to the changes observed in obstructive jaundice is best seen in the control series of cases of chronic cholecystitis shown in Table 4. In all of these, there was inflammatory disease in the right upper quadrant of the abdomen without icterus. Any differences between the findings in this series of cases and the three preceding may reasonably be ascribed to the effects of the bile retention.

CASE 7 (Case 67, Table 4).—*Chronic cholecystitis with cholelithiasis, hepatitis and pancreatitis (without obstruction).*—A woman, aged 46, was first observed Aug. 16, 1923. She had had epigastric distress for three years. The early history was not characteristic, but eventually the pain became more severe and was referred along the right costal margin and to the shoulder. In June, 1924, the pain was colicky, and the patient became slightly jaundiced during the next few days. When she was seen, July 8, there was no jaundice and the liver was not palpable. The serum bilirubin was 0.8 mg. and there was no retention of phenoltetrachlorphthalein. At operation chronic cholecystitis with multiple stones together with chronic appendicitis, hepatitis and pancreatitis was found. It was noteworthy that, with so extensive evidence of infection of the abdominal viscera including the liver, there should be no evidence of disturbance of the hepatic function revealed by the various tests.

CASE 8 (Case 58, Table 4).—*Chronic cholecystitis with cholelithiasis and pancreatitis (without obstruction).*—A man, aged 56, was admitted to the Mayo Clinic July 24, 1924. For twenty years he had had recurring attacks of colic in the upper part of the abdomen, with occasional attacks of slight jaundice and pale stools following the pain. In February, 1924, cholecystostomy was performed elsewhere and many stones were removed. Two months after the operation there was recurrence of the pain and the jaundice, associated with discharge of bile from the wound. The sinus persisted, and the pain and jaundice recurred periodically. At the time of admission there was no jaundice. The patient had lost a little weight. The liver was not palpable. The sinus was discharging bile and mucus. The serum bilirubin was 0.4 mg. and there was no retention of phenoltetrachlorphthalein. At operation the gallbladder was found to contain several small stones and was removed.

## DISCUSSION OF THE INDIVIDUAL TESTS

*Fructose Tolerance.*—Tallerman [8] has recently reviewed some of the difficulties incident to the use and interpretation of the results of the fructose tolerance test. He insists that the test shall not be considered positive unless the blood sugar reaches a value of 135 mg. or more for each hundred cubic centimeters, with a rise of at least 30 mg. in the sugar level. Our experience with normal persons has been similar to that of Tallerman, and we accept these criteria for a positive finding. At the same time, great care must be used in interpreting apparent deviations from this normal. In the presence of cholecystitis particularly, the possibility of an associated pancreatitis should be considered even in the absence of clinical diabetes.

In the twenty-eight tests performed on patients with uncomplicated obstructive jaundice, the fructose tolerance was definitely reduced in three instances. One of these patients had diabetes; in another evidence of pancreatitis was found at operation. In seven other patients, the blood sugar curve was suggestive, but did not fulfill the two criteria for a positive test.

Five patients with carcinoma of the head of the pancreas were studied; positive tests were obtained in three. The changes, however, may not have been entirely pancreatic in origin, for in one the fructose

8. Tallerman, K. H.: The Levulose Test for Liver Efficiency and an Investigation of the Hepatic Condition in Pregnancy, Quart. J. Med. **17**:37-52 (Oct.) 1923.

tolerance returned to normal following cholecystostomy and relief of the obstruction.

Of tests made on the group of patients with chronic cholecystitis, positive results were obtained in three. One of these patients had frank diabetes. A suggestive reaction was obtained in three other cases.

The fructose tolerance test apparently disclosed characteristic changes in experimental obstructive jaundice. Positive tests were not obtained clinically with any great degree of regularity in cases of obstructive jaundice. The additional difficulty of eliminating the possible effects of associated pancreatic disease have led us to question the clinical usefulness of this test.

*Blood Sugar Level.*—No significant disturbance in the fasting blood sugar level was observed in the present series of cases; in only one instance was it below 85 mg., a control case in which there had been a previous cholecystectomy but in which there was no direct evidence of active hepatic disease. In only two cases was the fasting blood sugar above 150 mg., and clinical diabetes was present in one of these. Obstructive jaundice apparently has no marked effect on the mechanism regulating the blood sugar level.

*Nitrogen Partition of the Blood.*—The changes in the nitrogen partition of the blood were in accord with the findings reported by Rowntree, Marshall and Chesney.[9] Retention phenomena were observed in one case in which renal insufficiency was a terminal event. The blood urea tended to be low in a certain percentage of these cases. In no case was it below 9 mg. The values lay within the lower range of normals, which perhaps was to be expected in view of the rather limited and often meat-free diet of many of the patients. The blood urea level on the average was apparently somewhat lower in the patients with icterus (from 22.5 to 28 mg.) than it was in those with cholecystic disease alone (32.3 mg.). This is in agreement with the observation that the blood urea level is reduced in dogs following the experimental ligation of the common bile duct. The changes observed in man, in our opinion, were not sufficiently well marked to be of clinical significance in the study of the individual patient, and the figures are not referred to in the case histories.

Bollman, Mann and Magath[10] find that following hepatectomy in dogs urea formation ceases, and in consequence they assert that the production of urea is entirely dependent on the liver. A comparable degree of hepatic insufficiency was not observed clinically. In Case 2,

9. Rowntree, L. G.; Marshall, E. K., Jr., and Chesney, A. M.: Studies in Liver Function, Tr. Am. Phys. **29**:586-625, 1914.

10. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, VIII, Effect of Total Removal of the Liver on the Formation of Urea, Am. J. Physiol. **69**:371-392 (July) 1924.

with a serum bilirubin of 16.2 mg., gross dye retention and an adequate urinary output, the blood urea rapidly rose from 30 to 146 mg. with the development of marked toxemia. This suggests that impairment of one function of the liver, as that of bile excretion, is not necessarily paralleled by impairment in the other physiologic activities of that organ.

There was no noteworthy change in the other nonprotein nitrogenous constituents of the blood studied. The total nonprotein nitrogen, uric acid, creatinin and amino-nitrogen came within the limits of the normal.

*Renal Function.*—Renal insufficiency has long been recognized as a postoperative complication of obstructive jaundice. Its importance has recently been emphasized by Walters and Parham [11] among others. Counseller [12] has been studying the morphologic changes in the kidney incident to bile retention. In general, however, in this series of cases we have not found evidence of serious renal damage apart from terminal or antemortem conditions. The normal phenolsulphonephthalein excretion serves further to emphasize the slight degree of impairment of renal function accompanying marked retention of bile. The majority of the patients with jaundice had varying degrees of albuminuria, usually slight, although casts frequently were present in the urine, but serious renal impairment was noted only as a terminal event.

*Bile Pigments.*—Icterus is the most striking single clinical manifestation in patients with obstructive jaundice, and of itself affords specific evidence of functional disturbance in either the formation or excretion of bile. Van den Bergh,[13] in particular, has pointed out what an important index the bilirubin content of the blood is to the degree of retention of pigment and to the clinical condition of the patient. Retention is evidenced in the blood before the development of the staining of the skin and sclerotics, characteristic of clinical icterus, and with the relief of obstruction the blood may return to normal before the disappearance of the color in the skin.

Patients with obstructive jaundice show an increase in the bilirubin content of the serum that is roughly proportional to the intensity of the staining of the conjunctivae. The highest value in this series of cases was 52.7 mg. per cent., more than twenty-five times the maximal normal value. There was no essential difference between the cases in which the obstruction was due to stone or stricture and those in which it was due to carcinoma in the head of the pancreas. In such jaundiced patients bilirubin is the preponderant serum pigment and the "icterus index" shows variations proportional to the bilirubin content. As pointed out

11. Walters, W., and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, Surg., Gynec. & Obst. **35**:605-609 (Nov.) 1922.

12. Counseller, V. S.: Personal communication to the authors.

13. Van den Bergh, A. A. H.: Der Gallenfarbstoff im Blute, Leiden, van Doesburgh, 1918, **8**.

in the previous paper, the "icterus index" is of less value in patients with normal or slightly increased serum bilirubin because other serum pigments, especially those of vegetable origin, as from carrots, may result in a high index and so simulate bile retention. The serum bilirubin values were normal in those patients with chronic cholecystitis. It should be emphasized that the latter were studied during quiescent stages. We have found that such patients (Case 59, Table 4) often have a slight increase in the serum bilirubin during acute attacks, and this has been further emphasized by de Takáts.[14] This increase may not produce sufficient discoloration of the skin or conjunctivae to be clinically recognizable as icterus, but the study of the serum bilirubin by demonstrating the presence of this "latent icterus" or bilirubinemia often is of great diagnostic value. The determination is relatively simple and rapid and deserves a prominent place among the laboratory aids in the study and diagnosis of jaundice.

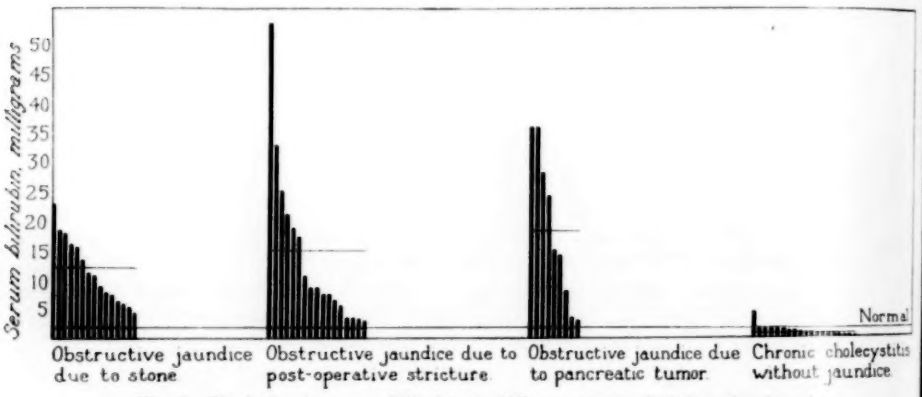


Fig. 3.—Variation in serum bilirubin in different types of obstructive jaundice. The maximal normal level is indicated, and in each group the average value is shown by the horizontal line.

*Phenoltetrachlorphthalein.*—In the presence of an actual obstruction to the common duct, the study of the excretion of phenoltetrachlorphthalein in the stools or by duodenal drainage is manifestly impossible. The study of the rate of removal of this dye from the blood stream, as advocated by Rosenthal,[15] greatly extends its clinical usefulness.

We have previously described the changes in the degree of dye retention following the experimental ligation of the common bile duct.

14. De Takáts, Geza: Latent Jaundice as a Symptom of Biliary Colic, Ann. Surg. **81**:108-110 (Jan.) 1925.

15. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, J. Pharm. & Exper. Therap. **19**:385-391 (June) 1922.

The changes observed clinically in cases of obstructive jaundice were similar. In all the cases of definite icterus there was marked dye retention. The maximal reading in the one hour specimen was 48 per cent., and in most cases it was 20 per cent. or more, in marked contrast to the maximal normal reading of 3 per cent.

The cases of cholecystitis without jaundice for the most part did not show dye retention. In six there was slight retention and the dye reading in the one hour specimen varied between 6 and 8 per cent. This was perhaps to be explained on the basis of an associated hepatitis. In all the others the dye readings were normal.

The excretion of dye in the urine furnishes valuable confirmatory evidence regarding the degree of retention in the blood. Normal persons and those with cholecystitis may excrete traces of dye in the two hour

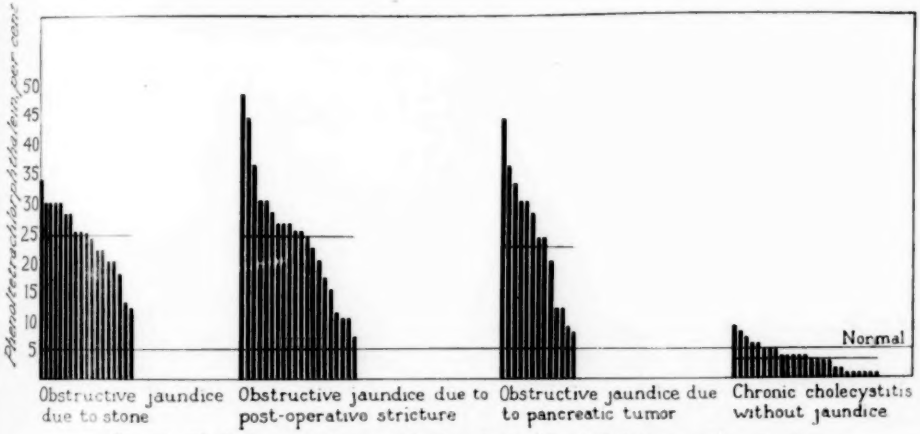


Fig. 4.—Variations in degree of phenoltetrachlorphthalein retention in the different types of obstructive joundice. The maximal normal level is indicated, and in each group the average value is shown by the horizontal line.

urine specimen following the injection. In no instance, however, did the urine contain more than 1 mg. of phenoltetrachlorphthalein without there likewise being marked dye retention in the blood stream.

## COMMENT

Frerichs,[16] in 1858, in his discussion of jaundice said:

> The bile which stagnates in the hepatic cells and bile ducts, in consequence of a mechanical impediment to its excretion, is carried into the blood by means of the veins and lymphatics. When the impediment has its seat in the ductus choledochus, the bile first shows itself after three days by a yellow color of

16. Frerichs, F. T.: A Clinical Treatise on Diseases of the Liver, New Sydenham Society of London, 1860, **1**:93.

the conjunctiva. Its absorption into the blood takes place much earlier; but in order that the jaundiced color of the skin should become visible, a certain amount of concentration is necessary. The color makes its appearance in the renal secretion sooner than it does in the skin, and the serous effusions in the various cavities of the body become tinged with pigment earlier than the urine. I have repeatedly found cholepyrrhin (bilirubin) in the serum of the blood and in effusions into the abdominal and thoracic cavities, where no traces of a jaundiced tint had been present either in the urine or in the skin.

Apart fom the tinging of its plasma, the blood undergoes no remarkable change from the absorption of bile; its proximate principles vary, as numerous analyses have shown, according to the constitution of the individual, and so forth, without presenting any constant abnormality.

Recent advances in biochemical methods permit us greatly to amplify this statement of Frerichs. A more detailed and exact study is now possible, but the conclusion is the same. Hepatic derangement results from bile retention in the body but, in general, serious disturbance of carbohydrate and protein metabolism has not been demonstrated. A diminished fructose tolerance is observed in a small proportion of cases and the blood urea level tends to be somewhat lower than usual, but the changes are not sufficiently striking to be of diagnostic import in any individual case. This result may also be inferred from the small amount of liver tissue found by McMaster and Rous [17] and others to be sufficient to support life.

While changes in the intermediary metabolism of protein or carbohydrate are difficult of demonstration, disturbances in other physiologic activities of the liver may readily be shown. The serum bilirubin and the phenoltetrachlorphthalein tests undergo characteristic changes. The close parallelism between the degree of bile retention and of dye retention in cases of experimental obstruction of the common duct has already been pointed out. Clinically there is much the same close relation between the intensity of the bilirubinemia and the degree of dye retention. Case 5 is of particular interest because, when first studied, the serum bilirubin was only slightly increased while the phenoltetrachlorphthalein test was normal. Following the development of obstruction, the serum bilirubin increased tenfold while there was marked dye retention. Case 4 is likewise of interest because, when first seen, there was a decrease in the dye retention associated with the complete disappearance of previous icterus. Later, following temporary obstruction and jaundice of only a week's duration, there was a definite increase in the degree of dye retention which became even more marked when complete obstruction developed. Case 3 is even more interesting because it was possible to study the whole cycle of changes associated with the development of obstruction and its relief.

17. McMaster, P. D., and Rous, P.: The Biliary Obstruction Required to Produce Jaundice, J. Exper. Med. **33**:731 (June) 1921.

The cases listed in the different tables show the stages in the return to normal following the operative relief of the obstruction. On the basis of our observations we may conclude that, immediately following the establishment of active biliary drainage, there is a rapid and progressive decrease in the serum bilirubin. Later the rate of removal becomes less rapid, and especially so if the prolonged jaundice has produced marked changes in the liver. As in Case 3, the serum bilirubin may be slightly increased over the normal for a considerable period.

The changes shown by the phenoltetrachlorphthalein test are similar to, but not identical with, those in the serum bilirubin. There is a rapid decrease in the degree of retention during the first few days. Thereafter there is a moderate degree of dye retention which is persistent, and the return to normal is very greatly delayed. During this period the degree of dye retention is greater than would be expected in comparison with the amount of bilirubinemia. The phenoltetrachlorphthalein findings may most readily be explained on the basis of the hepatitis described as occurring in cases of jaundice and observed at operation in many of the cases. The rapid changes immediately following the relief of the obstruction are perhaps evidences of a direct action of the retained bile on the liver. Experiments on the toxicity of bile, which will be reported later, apparently confirm this view. With the removal of the excess bile there is partial recovery, but the phenoltetrachlorphthalein test then indicates the persistent injury to the liver consequent on the jaundice.

The association of hepatitis with cholecystitis is well recognized. Graham [18] and MacCarty and Jackson,[19] among others, have described the lymphocytic infiltration and fibrosis present in the liver. These changes are most marked in the neighborhood of the gallbladder. It has been suggested that this hepatitis is responsible for the recurrence of symptoms in a small proportion of cases following cholecystectomy. The normal laboratory findings in the majority of the cases of cholecystitis, however, would indicate that this hepatitis does not produce any marked degree of functional disturbance.

We have stressed the close parallelism between the behavior of the serum bilirubin and the phenoltetrachlorphthalein in this series of cases. That the two readings do not have the same significance is shown by the behavior during the later portion of the recovery period. It is also demonstrated by the findings in cases of cirrhosis or carcinomatous involvement of the liver in which there may be marked dye retention without any bilirubinemia. These cases will be reported separately.

18. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521-537 (May) 1918.

19. MacCarty, W. C., and Jackson, Arnold: The Relation of Hepatitis to Cholecystitis, Minn. Med. **4**:377-382 (June) 1921.

## CONCLUSIONS

The greater number of tests of hepatic function studied fail to show significant, or sufficiently specific, changes to be of any great clinical value in the study of patients with obstructive jaundice. The fructose tolerance shows apparently characteristic changes following experimental obstruction to the biliary passages. Clinically, however, the results are too inconstant and the possibility of pancreatic effects too great for the test to be of value. The blood urea level, on the average, apparently is slightly lowered in cases of marked jaundice. This change again is too slight to be clinically significant in the study of any individual patient.

The most readily demonstrated changes in cases of obstructive jaundice are those in bile pigment metabolism. The icterus of itself is objective and conclusive evidence of disturbance in hepatic function. Changes in the serum bilirubin, however, precede the changes in the skin and conjunctiva. Accordingly, the determination of the serum bilirubin is the most sensitive and accurate index to changes in the degree of pigment retention, and so affords a quantitative guide to the progress of the jaundice. In addition, it permits the recognition of "latent icterus," which is of importance.

In cases of obstructive jaundice there is marked retention of phenoltetrachlorphthalein in the blood stream that roughly corresponds to the degree of bile retention. This apparently indicates primarily the effect of the bile retention on the liver. After the complete disappearance of the jaundice and return of the serum bilirubin level to normal, there frequently is a persistent slight degree of dye retention that apparently indicates the degree of residual hepatic disturbance remaining in consequence of the jaundice.

These two tests give promise of definite clinical usefulness in the study, and particularly the quantitative study, of the functional changes in patients with obstructive jaundice.

# THE AURICLES IN CASES OF AURICULAR FIBRILLATION *

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Although a remarkable advance has been made in recent years in the knowledge of the irregularities of cardiac rhythm and of abnormal cardiac rates and very definite ideas have been established in regard to the mechanisms that underly these abnormalities, very little has been added to the knowledge of the condition of the walls of the heart, especially of the auricles, which might be a factor in producing some of these disturbances in rate and rhythm. Many of these abnormalities in cardiac rate and rhythm are associated with disturbance in the normal action of the auricles, and still in most pathologic reports on the heart there is very little information given in regard to the condition of the auricular walls as compared with those of the ventricles. It is hoped that in the future pathologists will include in their routine description of the heart some information in regard to the degree of dilatation of the auricles, the thickness of their walls, and both the gross and the microscopic appearance of the muscle and other tissue in the walls of the auricles. This study was undertaken in order to find out if, in cases with auricular fibrillation, any lesions could be detected in the auricles which might be considered as a factor in the production of the fibrillation or as a result of it.

Before the nature of auricular fibrillation was as well undersood as it is at present, a few workers had described lesions in the walls of the auricles in hearts with irregular rhythm. Among them Radasensky [1] in 1895 reported the appearance of fibrosis in the walls of the auricles in six cases in which the cardiac rhythm was irregular. Also, in 1899 Dehio [2] described fibrosis in the right auricle of hearts that had shown irregularity.

A few years later, as the polygraph began to show what was happening in the heart during auricular fibrillation, it was thought that the condition might be associated with some lesion in the neighborhood of or at the sino-auricular node, and the attention of several workers was directed to this region of the heart. As a result, Schönberg,[3] Cohn and

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1. Radasensky: Ztschr. f. klin. Med. **27**:381, 1895.
2. Dehio: Deutsch. Arch. f. klin. Med. **62**:1, 1899.
3. Schönberg: Frankfurt. Ztschr. f. Path. **2**:153, 1909.

Lewis,[4] Falconer and Dean,[5] Draper[6] and Hume[7] all reported the presence of some lesions in this region. No one of these workers reported any characteristic acute lesion. In general an increase in connective or fatty tissues, chronic changes of the blood vessels or some infiltration with leukocytes were the lesions described. Price and McKenzie,[8] on the other hand, did not consider that there was any more fibrosis in the region of the sino-auricular node in cases with auricular fibrillation than in those in which the cardiac rhythm was regular. In addition, Southerland and Coombs[9] reported the presence of fat throughout the auricular musculature and an increase in endothelial cells in a case of auricular fibrillation associated with an acute infection. In this case, similar lesions also were present in the walls of the ventricles.

Apparently, interest in the attempt to put the cause of auricular fibrillation on an anatomic basis waned after these few studies, because one finds very little on this subject in the literature after 1914. Possibly this was due to the fact that subsequent studies on the nature of auricular fibrillation showed that it was not clear just what was going on and that very likely the trouble might not be with the sino-auricular node. Cohn,[10] in Nelson's Loose Leaf System of Medicine, says that the pathologic lesions reported in the sinus region in cases of auricular fibrillation are not striking. He also mentions that the transient nature of auricular fibrillation in some cases suggests that there is no chronic organic lesion as the underlying cause.

Although at the present time it has not been definitely established in just what way fibrillation of the auricles begins and why it continues, a good review of the subject has been prepared by Garey[11] which brings out the various theories that have been advanced to account for the condition. In auricular fibrillation disturbances may occur in the pacemaker so that an abnormal number of impulses are sent out to the auricular muscle, or the control of the heart beat may be taken over by some other than the normal pacemaker. In addition, the conduction system for impulses in the auricular wall may be functioning in an abnormal manner. There has not been described any special tissue in the auricles for the transmission of impulses so it is presumed that the muscular tissue is the pathway along which travel the impulses to set off the muscular contractions. Finally, the muscle tissue itself in auricular

4. Cohn, A. E., and Lewis, T.: Heart **4**:15, 1912-1913.
5. Falconer, H. W., and Dean, G.: Heart **4**:87, 1912-1913; ibid. **3**:247, 1911-1912.
6. Draper: Heart **3**:13, 1911-1912.
7. Hume, W. E.: Heart **5**:25, 1913-1914.
8. Price, F. W., and McKenzie, I.: Heart **3**:233, 1911-1912.
9. Southerland, G. A., and Coombs, C. F.: Heart **5**:15, 1913-1914.
10. Cohn: Nelson's Loose Leaf System of Medicine **4**:333, 1920.
11. Garey: Physiol. Rev. **4**:215, 1924.

fibrillation may be in some way disturbed so that it does not respond to the stimuli in the usual manner. It is obvious therefore that with our present knowledge there is no one place in the auricles to which one might turn with the hope of finding a lesion to account for auricular fibrillation.

In this work, therefore, an attempt was made to study the auricles in the region of the sino-auricular node in order to see if there were any lesions about the pacemaker, and also to study the muscular tissue in other parts of the auricle in order to pick up, if possible, any lesions of the muscle that might be a factor in disturbing the passage of impulses or the response of the muscle to impulses. If any lesion should appear generally distributed throughout the muscle, it might, of course, be the result of auricular fibrillation and not a factor in the production of the condition. By a study of the relation of such a lesion to the duration of the auricular fibrillation, some idea might be formed as to whether a diffusely scattered lesion was the result or cause of the irregularity. Attention also was paid to the age of the subject as well as to the duration of the auricular fibrillation in order not to confuse lesions due to advancing years with changes in the auricular wall which might be the cause or result of this irregularity. In addition, the gross appearance of the auricles in regard to their size and the condition of their walls, as well as the size of the heart as a whole and any valvular defects or lesions in the ventricular walls, were studied in order to find if any peculiarities along these lines were associated with auricular fibrillation with sufficient constancy to be thought a factor in its production. As so little is described about the condition of the auricles in reports of necropsies, it was felt that careful control material representing similar ages to those of the patients with auricular fibrillation should be studied. In this work the material from control cases represented both acute and chronic disease.

The gross appearance of the cavities of the auricles, the thickness of the walls, the weight of the hearts and any valvular defects or lesions in the ventricular walls were noted in this compilation of cases. For microscopic study, tissue was taken from the region of the sino-auricular node, that is, between the entrance of the superior vena cava and the right auricular appendage and from the septum between the two auricles in the region of the foramen ovale, usually between the foramen and region of the sino-auricular node. In addition, a piece of the wall of the left auricle between the entrances of the pulmonary veins was studied and also a bit of tissue from the left auricular appendage. The tissues for microscopic study were fixed either in Zenker's fluid or 10 per cent. formaldehyd solution and stained by eosin and methylene blue or hematoxylin and eosin, respectively, depending on the fixative.

In the group of cases that were studied there were eleven cases of auricular fibrillation associated with both acute and chronic diseases. In seven of these cases, the heart had been in constant auricular fibrillation for several days at least before death, and in one instance the auricular fibrillation had been present for several years. In three of the cases, the auricular fibrillation was a transient affair and in one instance apparently just a terminal phenomenon. The age of the subjects with auricular fibrillation varied from 21 years to over 70. The patient with fibrillation as a terminal event was just past 50 years of age, and the three patients with transient auricular fibrillation ranged from 40 to over 70 years of age. For comparison with these eleven cases with auricular fibrillation there were studied in a similar manner twenty-three others in which the heart action was regular. The ages of the control patients varied from 10 years to over 70 years, and they suffered from a variety of acute and chronic diseases.

Unfortunately, in many of the necropsy protocols no mention was made of the gross appearance of the auricles and, therefore, in these cases it had to be assumed that the auricles were approximately normal in appearance. It is appreciated that it would have been more satisfactory if an actual statement had been made that the auricles appeared normal, but there were sufficient notes on the abnormal appearance of the auricles in certain cases to justify the belief that if there had been anything striking in their appearance a note would have been made of it.

In the group of prolonged fibrillators, four of the seven cases presented evidence of dilatation of one or both auricles, but in the other three no mention was made of dilatation. In the four cases in which the auricular fibrillation was more transient in character, a dilatation of the right auricle in one instance was the only mention of that gross lesion. Of course, there may be several factors which can lead to auricular fibrillation, and dilatation of the auricles may be this factor in certain cases, but it seems quite evident from the foregoing figures that dilatation of one or both auricles is not essential to the production of this type of cardiac irregularity. That dilatation of the auricles may occur without auricular fibrillation is, of course, well known, and this was confirmed by the control cases in which seven out of twenty-three showed dilatation of one or both auricles.

In only three of the eleven cases of auricular fibrillation was any appreciable abnormality of the walls of the auricle recorded. In one of these three, the walls of both auricles were thought to be thinner than normal, in another the right auricular wall was thickened, and in the third the left auricular wall was described as thickened in one place and thinner than usual in another. Certainly with these meager findings which are also quite variable, one is not justified in concluding that

there is any gross disturbance in the auricular wall as yet described that is a factor in the production of auricular fibrillation.

The weight of the heart as a whole was not essentially different in the cases with auricular fibrillation from the other cases. The weights of the hearts with the more prolonged fibrillation varied from 410 to 700 gm., with an average of 546 gm., which indicated a moderate enlargement. In the cases with more transient fibrillation the hearts varied from 240 to 520 gm., with an average of 357 gm. There is certainly nothing unusual enough about these weights to indicate that there is any relation between the size of the heart and this type of irregularity.

In this group with auricular fibrillation, there also were no lesions of the valves or myocardium of the ventricles which occurred with sufficient regularity to justify a belief that they are essential to the production of this type of irregularity. In the seven cases of more prolonged fibrillation, the valves and musculature of the ventricles were reported as normal in four. In one there was marked disturbance of the valves; in another there were chronic changes in the myocardium of the ventricles, and in the third an infarction of the wall of the ventricle. In the cases with more transient fibrillation, one of the three showed chronic changes in the musculature of the ventricular walls due to coronary disease, but in the other two there was no apparent chronic disease of the ventricular muscle or of the valves. In one of these two, there were yellowish streaks in the cardiac muscle, presumably due to the general sepsis that was present.

On the whole, with the data accumulated from these cases it is quite evident that there is no gross lesion in the heart that is essential to the production of auricular fibrillation. Although it is evident from clinical observation that stenosis of the mitral valve with subsequent dilatation of the auricles is often associated with fibrillation of the auricles, this irregularity was present in this series often enough without any valvular disease or dilatation of the auricles to rule out these conditions as essential.

In taking up the microscopic study of the tissues from the auricles, attention was first focused on the sino-auricular node region in order to see if any of the lesions described by the earlier workers could be found. In comparing the cases with fibrillation and those without in patients of the same age, it was quite apparent that there was no increase of connective tissue or definite scar formation in the tissues from the sino-auricular node region, and as far as could be determined the tissue that was thought to be the nodal tissue appeared the same in the fibrillators as in the controls. So far as the arteries were concerned there were some sclerotic changes in the blood vessels in certain cases, but these changes seemed to be related to the age of the patient and occurred

just as often in the cases without auricular fibrillation as with it. There was considerable edema of the tissues in this region in some instances, but it was not present in the majority of the cases with auricular fibrillation and also it was present in some of the controls. In the muscle tissue itself there was no lesion peculiar to this region, although a lesion did occur here as well as elsewhere in the muscle tissue of the auricles which will be described below. This lesion in the muscle tissue was present more often in the cases with auricular fibrillation than in the controls. In nine out of the eleven cases with fibrillation this degenerative lesion of the muscle was present. In fifteen control cases representing the same periods of age, this degenerative lesion in the muscle was only present in four instances. It is apparent therefore that this lesion in the muscle occurs more frequently in cases with auricular fibrillation than in cases without it. Although in a few instances there was some invasion of the connective tissue in this region by endothelial cells and leukocytes, it did not occur any more often in the cases with fibrillation than in the controls and in many instances was apparently associated with the other pathologic conditions present in the case; it therefore presumably was not of importance in regard to the cardiac irregularity.

These cases did not support the views advanced by most of the previous workers that there was a definite lesion in the region of the sino-auricular node in cases of auricular fibrillation. In the walls of the auricles away from this node there seemed to be no appreciable difference whether the tissue was taken from the left auricle or in the septum between the auricles. In general, the tissue taken from the left auricular appendage did not show quite so much as the other bits of the auricles in those instances in which some lesion was present in the muscle. Except for an occasional lesion that was obviously associated with the disease from which the patient suffered, irrespective of the cardiac condition, the abnormalities in the tissues were the same as those seen in the region of the sino-auricular node and occurred with the same relative frequency among the fibrillators and the controls. The interesting lesion in these cases was the one in the muscle fibers that was mentioned above.

The lesion that was generally distributed throughout the muscle of the auricles in certain cases varied considerably in intensity in the different cases. The slightest abnormality noted was an edema of the muscle fibers with vacuolization and some slight changes in the staining reaction of the fibers which suggested degeneration. When the process was more pronounced, the vacuolization increased, the striations in the fibers disappeared in part, and the changes in the staining reaction increased. The nuclei of the muscle fibers showed very little, if any, change and the disturbance in the fiber did not necessarily extend

throughout the whole of the individual fiber. In the instance in which the fibers showed the most marked disturbance, actual necrosis of part or all of the fiber took place and cellular reaction with phagocytes invading the muscle was in some instances present. It is rather striking how little if any cellular reaction was present in the milder forms of this degeneration of the muscle fibers. No evidence of appreciable reaction on the part of the supportive connective tissue framework was observed, nor was there any acute lesion made out in the blood vessels. In some instances there was marked interstitial edema as well as the lesion in the muscle. However, this interstitial edema occurred in other cases in which the lesion in the muscle was absent, so there may be no relation between the two. It seems probable that these various lesions are all different stages of the same process but, of course, it cannot be absolutely established that they are not the result of different causes. Just what the end-result of this degenerative lesion in the muscle will be could not be determined from these cases.

It is difficult to decide whether this degenerative lesion in the auricular muscle bears any relation to the production of auricular fibrillation or might result from it. The lesion does occur without auricular fibrillation but not with anywhere near as much frequency and not to such a marked degree. On the other hand, in two out of the eleven cases with fibrillation this lesion was not found. This lesion does not seem to represent a disturbance of old age, for in one case with auricular fibrillation of long standing in a patient over 70 years of age the lesion was not found; the lesion was present, however, at all ages among the fibrillators, and among the controls it was not confined to the older patients. That there is some relation between auricular fibrillation and this lesion is suggested by the frequency with which it was found in these cases in comparison to its occurrence in regularly beating hearts, but it may as well be the result of the auricular fibrillation as a factor in its production.

From the study of this small group of cases it was evident that there was no typical lesion in the auricles that could be looked on as the cause of auricular fibrillation. A slight degenerative lesion was found in the muscle fibers of the auricles much more frequently with auricular fibrillation than in regularly beating hearts of the same age. It is interesting to speculate whether this lesion was the result of the irregularity of rhythm or a factor in its production, by causing some defect in the conduction of impulses or in the ability of the muscle to respond to the impulses.

# VENOUS PULSE PRESSURE

## A CLINICAL NOTE *

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In a recently published study of the centripetal venous pulse in man, White [1] discusses the unfruitful efforts to measure the pulse pressure in the veins. The residuum of pressure from the arterial side would appear insufficient to affect manometric readings through the intravenous cannula, in his judgment. Furthermore, the success of White's observations on the centripetal venous pulse depends on a proper equalization of pressure within the glass capsule with the diastolic venous pressure. The difficulties encountered in this direction warrant recounting the following case:

### REPORT OF CASE

E. G., a male student, aged 23, was admitted to the University Infirmary, March 28, 1924, in marked cardiac decompensation, manifested by persistent vomiting, dyspnea, cyanosis and palpitation. The underlying cardiac condition, which had existed for eleven years, consisted of double aortic and double mitral lesions. March 29, the symptoms of cardiac embarrassment became more pronounced and the venous pressure registered 18 cm. of water. A venesection of 16 ounces (473.1 c.c.) was performed, with a fall of the venous pressure to 8 cm. and marked general improvement. The arterial blood pressure was 160 mm. systolic and 20 mm. diastolic. For the first time a positive centripetal pulsation in the veins on the back of the hand became apparent.

The advantage gained by venesection was maintained. The venous pressure did not subsequently exceed 12 cm. in spite of a complicating pericarditis which intervened April 1. The centripetal venous pulse continued until April 6. April 5, complete occlusion of the vein under observation was obtained at 12 cm. The vein collapsed at 8 cm., but with each systole there was a visible pulsation in the studied segment of the vein until a pressure of 12 cm. was reached. Both end points were very distinct and were repeatedly confirmed.

This observation was interpreted to mean that during the cardiac systole a pressure of 12 cm. of water existed in the peripheral veins and that on diastole this pressure fell to 8 cm., giving a venous pulse pressure of 4 cm. Obviously several factors, such as fever, heightened the venous pressure, and a dilated vascular bed in the presence of the excessive pulse pressure of aortic regurgitation combined to make such an observation possible in this subject, since repeated studies have failed to duplicate the foregoing findings. Indeed, the same subject four months later, having recovered his accustomed degree of cardiac compensation, did not show even the Quincke centripetal venous pulse.

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* From the University of Wisconsin Medical School.

1. White, H. L.: Arch. Int. Med. **35**:124 (Jan.) 1925.

# Book Reviews

La Sifilide Ignorata e Strana. Second Edition. By Prof. C. Martelli. Naples: V. Idelson, 1923.

This valuable treatise belies its name. It not only deals with the rarer manifestations of syphilis, but also covers the entire subject.

The first half of the book consists of an orderly presentation of our present knowledge of the disease; the remainder is taken up with the more unusual types. The method is excellent from the standpoint of the student, as all but the barest outline of the clinical manifestations of the disease is included in the second portion, which is classified by anatomic systems. This has enabled the author to paint an unusually clear and vivid picture of the routine case in the first section, unencumbered by detail and variants.

The laboratory side of the problem is excellently presented, the sections on the spirochete, the Wassermann and other serologic and chemical tests being unusually clear and concise. In this connection, I wonder how many of us would dispose of the Lange colloidal gold reaction in a single sentence as "superfluous." The chapters on therapy cover not only the routine drugs used but also a thorough review of the chemotherapy of syphilis with a large variety of substances both old and new. Martelli is partial to the use of iodids, uses both inunctions and injections of mercury as a routine, and pushes the arsenicals rather heroically, not hesitating to give intramuscular injections in many cases. In the case of very young children, he leans toward conservatism. After his statements concerning the inability of the stomach to deal with adequate amounts of mercury in the adult, the prescription on Page 215, intended for the oral chemotherapy of children, seems rather fantastic.

In the second portion one might well take exception to much of the pathology described as syphilis. Diseases in patients with positive Wassermann reactions are not necessarily syphilitic, even though the patients do recover under antisyphilitic treatment. This is presumptive evidence that will not satisfy most scientists. There are 136 cases described in the volume as examples of disease. The author seems fully cognizant of the dangers of this method and speaks of "pansifilistas" whose enthusiasm induces them to ascribe all pathologic conditions to the spirochete. However, as a horrible example of this tendency, he quotes a case of frank syphilis, in which the patient developed inflamed joints, but declares that it was only rheumatism, because the patient recovered under salicylates! It is only fair to state, however, that most of the illustrative material is genuine, many cases being checked by operation, necropsy or other incontrovertible evidence.

The book is illustrated with many excellent photomicrographs and drawings, some in colors, but is marred by the inclusion of some wretched sketches of intravenous injections and a few poor photographs.

The indexing is excellent, and a very elaborate classified bibliography is included. The latter is noticeably lacking in references to the English and American literature.

Pernicious Anemia and Aplastic Anemia. By Arthur Sheard, M.D. A Thesis Presented for the Degree of Doctor of Medicine, University of Leeds. New York, William Wood & Co., 1924.

A detailed study is given of fifteen consecutive cases of pernicious anemia, one of hemolytic jaundice and one of aplastic anemia, and a review of ninety cases of pernicious anemia in the Leeds General Infirmary in the preceding ten years.

In the cases of pernicious anemia, the cord changes, achlorhydria and bone marrow changes are discussed in particular detail and the other features are

adequately considered. The author concludes that it is caused by an infectious agent in the gastro-intestinal tract, occurring only in subjects with achlorhydria. This is contrary to American ideas, as some cases of advanced pernicious anemia may retain a practically normal gastric acidity.

Aplastic anemia, the author believes, belongs to a pathologic syndrome, occurring either secondarily to toxic factors or primarily. It bears no relation to pernicious anemia. It may occur in all grades of severity and may show equal or disproportionate deficiency in the three blood elements, erythrocytes, leukocytes and platelets. Blood transfusions offer the only remedial hope.

PRECIS DE CLINIQUE SEMIOLOGIQUE. By GASTON LYON. Paris, Masson et Cie, 1924.

This excellent volume should make a good practitioner of its careful readers. While not pretentious, it takes up in a careful, systematic way the examination, diagnosis and treatment of patients. Beginning with a detailed chapter on history taking, physical examination and laboratory examinations, the author gives numerous valuable points with their significance clearly indicated. A detailed outline of system examinations follows, with interpretation of findings, special consideration being given to the diagnosis and the cause of symptoms. The digestive, repiratory, circulatory, urinary and nervous systems are dealt with at length. Prognosis receives careful consideration and the question of complications is well presented.

The detailed consideration of therapy includes chemical, physical, surgical, as well as colloidal, glandular and psychiatric methods. A chapter on the action of medicines follows, and the necessity of choosing the appropriate one from a number of possible drugs is emphasized.

Throughout is emphasized the need for careful and accurate study to determine not merely the diagnosis, such as pharyngitis, but also the underlying cause of the malady.

JAHRESBERICHT ÜBER DIE GESAMTE INNERE MEDIZIN UND IHRE GENZGEBIETE. Berlin, Julius Springer, 1921.

This is an annual bibliography covering the entire field of internal medicine and biology. The major fields covered are: general physiology and biology; pathology, diagnostic and symptomatic; therapy; pharmacology and toxicology; infection and parasitology; serology and immunity; metabolism; internal secretions, and a classification by systems of: the digestive tract; liver and gallbladder; pancreas; spleen; urinogenital tract; blood; circulation; respiration; locomotion, and the neurologic system.

The volume is seven hundred and twenty pages. The references, predominantly German, include some American and French, but relatively few others.